Feasibility of Serial Neurocognitive Assessment Using Cogstate During and After Therapy for Childhood Leukemia

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Abstract

Purpose: Neurocognitive impairment is frequently observed among survivors of childhood acute lymphoblastic leukemia (ALL) within the domains of attention, working memory, processing speed, executive functioning and learning and memory. However, few studies have characterized the trajectory of treatment-induced changes in neurocognitive function beginning in the first months of treatment, to test whether early changes predict impairment among survivors. If correct, we hypothesize that those children who are most susceptible to early impairment would be ideal subjects for clinical trials testing interventions designed to protect against treatment-related neurocognitive decline.

Methods: In this pilot study, we prospectively assessed neurocognitive functioning (attention, working memory, executive function, visual learning, and processing speed), using the Cogstate computerized battery at six time points during the 2 years of chemotherapy and 1 year post treatment enrolled on or as per Dana-Farber Cancer Institute ALL Consortium protocol 11-001; NCT01574274.

Results: 43 patients with ALL consented to serial neurocognitive testing. Of the 31 participants who remained on study through the final time point, one year after completion of chemotherapy, 28 (90%) completed at least five of six planned Cogstate testing timepoints. Performance and completion checks indicated a high tolerability (≥88%) for all subtests. One year after completion of treatment, 10 of 29 patients (34%) exhibited neurocognitive function more than 2 sd below age-matched norms on one or more Cogstate subtests. **Conclusions:** Serial collection of neurocognitive data (within a month of diagnosis with ALL, during therapy and one year post treatment) is feasible and informative for evaluating treatment-related neurocognitive impairment.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. Although current cure rates exceed 90% for most groups[1], treatment frequently induces measurable neurocognitive deficits [2–13] even when it does not include prophylactic cranial radiation, with a significant impact on survivors' quality of life[14–16]. Children treated for ALL exhibit increased rates of impairment in discrete neurocognitive and behavioral domains, including attention and working memory, processing speed, and executive functioning [6, 15, 17–27], which may reflect accelerated central nervous system aging[28]. Deficits evident at the completion of treatment can persist and continue to deteriorate over decades [17, 19, 29, 30], causing learning disorders[17, 21, 22, 24, 25, 30, 31] and greater need for special education[32], along with decreased rates of graduation[19, 33], employment[34], and independent living[35]. These adverse treatment sequelae commonly produce significant life-long impact upon patients and their families, in addition to a measurable cost to society.

The pathophysiology of chemotherapy-induced neurocognitive impairment (CICI) is multifactorial, and appears to relate to some or all of the following processes: induction of oxidative stress and neuroinflammation, perturbations of folate physiology, epigenetic changes, and direct injury to neuronal, glial and/or endothelial structures.[36] Elimination of the causative chemotherapeutic agents is not a viable means of reducing CICI, as an increase in leukemia relapse would be the inevitable result. Fortunately, emerging data suggest that pharmacologic intervention might ameliorate or prevent CICI by inhibiting one or more of the causative pathways[37–39], particularly if the intervention can be initiated early in the two to three-year course of leukemia therapy, before CICI becomes clinically significant.

To maximize the risk-benefit ratio of a clinical trial testing a preventive strategy, we sought to develop methods to identify children with ALL who are most susceptible to CICI, as well as to determine the earliest time point during therapy when CICI could be detected. This pilot study was undertaken to demonstrate the feasibility of longitudinal measurements of neurocognitive functioning as well as analysis of paired biomarkers within cerebrospinal fluid (CSF). We previously reported that Cogstate, a validated, reliable, non-invasive measure of neurocognitive functioning, can be reliably conducted at multiple institutions participating in a cooperative group trial, and that neurocognitive function measured during the first three weeks of leukemia therapy is a stable baseline from which to identify subsequent treatment-related changes[40]. In addition, cerebrospinal fluid can be reliably collected, processed, shipped, and analyzed with no loss of biomarker stability, and those samples collected during the initial four-week Induction phase are within expected norms, indicating a reliable baseline for detecting treatment-induced changes.

In this follow up report of the pilot cohort, we describe the feasibility of longitudinal assessments of neurocognitive functioning, as measured by Cogstate, at five points during the 25 months of therapy for childhood ALL, as well as a sixth evaluation one year after completion of all planned therapy.

Methods

Subjects

Patients between the ages of 5–21 years with ALL, enrolled on, or treated according to, Dana-Farber Cancer Institute (DFCI) ALL Consortium protocol 11 – 001, "Randomized Trial of IV SC-PEG asparaginase and IV Oncaspar in Children with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma" (ClinicalTrials.gov identifier NCT01574274)[41] were eligible for a companion study "Serial Neurocognitive Screening of Children and Adolescents During Treatment for Acute Lymphoblastic Leukemia (ALL) on the DFCI ALL Consortium Study 11 – 001". Patients known to have any of the following conditions were excluded: active meningitis; poorly controlled seizures, neurodevelopmental disorder (e.g., autism) that would prevent completion of Cogstate testing, congenital condition associated with intellectual disability (e.g., trisomy 21), or serious concomitant systemic disorders (including active infections) that would compromise the patient's ability to complete the study. Patients were enrolled at four sites in the consortium: Dana Farber Cancer Institute, Boston MA; Montefiore Medical Center, Bronx, NY; Columbia University Medical Center, New York, NY; and Hasbro Children's Hospital, Providence RI. The institutional review boards of the treating institutions approved both clinical protocols. Informed consent was provided by the subjects' guardians or by those patients over the age of 18 years. Written assent was provided if age-appropriate, following institutional guidelines.

Measures

The Cogstate battery

Cogstate is a battery of computer-based tests selected specifically to assess domains of neurocognitive function that have been previously found to be impaired among childhood leukemia survivors.[40] Participants completed each 20-25-minute computerized neurocognitive evaluation supervised by a research team member. Participants' neurocognitive performance was assessed over time using the Cogstate test battery, at baseline (within the first 3 weeks after diagnosis) and again at 5 additional post treatment time points (Table 1). The Cogstate battery yields five cognitive domain scores: Continuous Paired Association Learning Task (CPAL, visual memory, total number of errors), Detection Task (DET, timed psychomotor function), Groton Maze Learning Task (GML, novel problem solving/error monitoring, total number of errors), Identification Task (IDN, timed attention/vigilance), and One Back Task (ONB, timed working memory task). The timed tasks were measured in log milliseconds so that a shorter raw response time represented better performance.

Performance and Completion analysis

Performance and completion check criteria were used to evaluate feasibility, that is, the extent to which the Cogstate battery was well tolerated and completed in full by a pediatric oncology population. Successful performance was defined as completing each test in a manner that complied with test requirements. Performance check criteria were specified a priori in order to identify scores that indicated either the participant did not understand the test instructions or was not cooperative. Performance check criteria are derived statistically such that when trained and supervised appropriately, the relevant study population will achieve the said criterion for the respective task 90% of the time when they are demonstrating the appropriate level of effort.

Cognitive Assessments Scoring

Raw scores for all outcome measures (i.e., CPAL, DET, GML, IDN, and ONB) were standardized into *z*-scores based upon age normative data and rescaled when appropriate, so that a higher standardized score always represented a better outcome. The score is calculated by subtracting the predicted value from the regression curve for the patient's age and the observed value then dividing the predicted standard deviation (SD) for that age. The mean of such *z*-scores from the age matched control population will be zero. Individual patient *z*-scores will provide an estimate of deviation from the control's age norms, and the mean *z*-scores from patient groups will reflect the extent to which those patients, as a group, demonstrate pathology independent of their ages. Data were presented using raw and *z*-scores. The *z*-scores were also dichotomized as either below normal limits or impaired, as defined by whether or not their *z*-score was 1 and 2 SDs or more below their age norm, respectively [42].

Statistical Analysis

Descriptive statistics were used to report the patient's baseline characteristics, cognitive assessments, and distribution of impairment.

Two-sample *t*-tests were used to compare the changes of cognitive scores from baseline to the CNS-directed phase of treatment (i.e., approximately 3 months since baseline) as well as from baseline to post-treatment (i.e., approximately 1 year after completion of chemotherapy and 3 years after the baseline assessment). Wilcoxon rank-sum tests were used instead for skewed outcomes. Specific hypotheses were evaluated using two-sample *t*-tests, for example, the changes in cognitive performance between boys and girls, between age groups, CNS prophylaxis – irradiation, and the median household income by patient's zip code.

Exploratory analyses were carried out on the profiles of cognitive performance over time using latent class growth mixture modeling (LCGMM) [43]. LCGMM is designed to model each child's unique growth curve over time, often used to find similarities between growth patterns by fitting a unique growth trajectory per child. It is part of the broad literature of growth mixture models [43]. We explored whether or not children experienced an initial drop in neurocognitive performance, as well as additional analyses examining the individual rate of recovery or decline over time. The subgroups of children's growth trajectories may be sufficiently similar so that these growth patterns can be aggregated into a common trajectory shared by members of the sample subgroup. The main purpose of LCGMM was to identify a subgroup of children whose growth pattern diverges early from most children in the sample. LCGMM uses all available observations per person, assuming missing at random. While, we were also interested in linking the patterns of growth trajectories against known risk factors, our sample size was not large enough for these sub analyses.

Results

Forty-three participants consented to participate on this neurocognitive sub-study (Fig. 1). Twelve came off study prior to time point 6 for the following reasons: induction failure, n = 3; CNS and/or marrow relapse, n = 3; death, n = 2; intercurrent illness preventing completion of Cogstate testing, n = 2; loss to follow-up or transfer to another institution, n = 2). These 12 patients completed a median of 2.5 Cogstate points (Range 1–5). Of the 31 patients who remained on-study until one year after completion of chemotherapy, 22 (71%) completed all timepoints 1–6, 6 (19%) completed 5 of 6 time points, and 3 (10%) completed fewer than 5 time points.

Review of the completion rates indicate that 100% of subjects completed the Detection, Identification and One Back tests in full. Completion rates were slightly lower for the CPAL (95%) and GMLT (88%). Performance checks exceeded 90% for all tests in the battery aside from Detection (88%).

Baseline Characteristics

Table 2 presents descriptive statistics of demographic and clinical characteristics of the total sample of N = 43 children. The patients' age ranged from 5 to 19 years with a median age of 9 years; 28 (65.12%) were male; 29 (67.44%) were categorized as high risk determined by NCI criteria and biological features; 33 (76.74%) received intrathecal chemotherapy only as prophylaxis against CNS relapse while 10 (23%) also received 1200–1800 cGy cranial irradiation for CNS

prophylaxis due to protocol criteria (T-cell immunophenotype, overt CNS involvement at diagnosis, or very high risk of relapse); the median household income in the patients' zip codes ranged from $24,421 to $212,394 with a median of $74,713.

Performance over time

Table 3 summarizes the raw score means and Fig. 2 displays the distribution of the patients' Cogstate brief battery cognitive assessments over time at baseline (i.e., start of Induction), Consolidation I (5 weeks), CNS therapy (7 weeks), Consolidation II (18 weeks), Continuation (62 weeks), and 1-year after completion of treatment (approximately 161 weeks). Mean scores did not differ significantly from normal, with modest fluctuation in distribution over the treatment phases. Comparatively, across the assessments, CPAL, DET, and GML observed larger outliers compared to IDN and ONB.

Mean Difference in Raw Scores Over Time

Table 4 shows the mean difference in raw scores from Induction to (1) CNS therapy and (2) post-1 year treatment. The executive functioning performance on the GML test for older patients (9–19 years old) – $t(13.61) = 3.51$, $p = 0.004$ (CNS therapy-Induction difference) and $t(20.91) = 2.69$, $p = 0.014$ (post-1 year treatment-Induction difference) and males – $t(18.32) = 2.47$, $p = 0.024$ (CNS therapy- Induction) – yielded statistically significant improvements. All other comparisons were not statistically significant.

The Groton Maze Learning (GML) task appears to be the most sensitive to change over time. Specifically, the GML task identified that those patients between the ages of 5–8 years older performed worse over time than those aged 9–19 between the baseline assessment in Induction and the CNS phase (p = 0.004), and from baseline to 1-year post treatment (p = 0.014). Additionally, females performed worse over time on this GML task than males over the identical time frame (p = 0.024). Of note, there was also a trend for females to perform worse over time than males over the same time frame on the CPAL task between Induction to the CNS phase (p = 0.054).

Neurocognitive Impairment

Table 5 displays the proportion of patients who performed either within the impaired range (as defined by being 2 SD below the population age mean) or outside of normal limits (defined as being below 1 SD of the population age mean) over time. One year after completion of chemotherapy (timepoint 6), 15 of 29 participants (52%) had z-scores one or more SD below age norms on one or more Cogstate subtest. Ten of 29 (34%) exhibited abnormal neurocognitive function with z scores at least 2 SD below age norms in at least one subtest.

Descriptively, a higher proportion of subjects performed within the impaired range group at the 2 SD threshold during the post 1-year treatment respective to the prior time points: CPAL (N = 4; 14%), DET (N = 5; 17%), GML (N = 2 7%), IDN (N = 3; 10%), and ONB (N = 2; 7%), which also exceeds the normative distribution expectation of 2.3% to be below 2 SD of the mean. At below the 1 SD threshold, patients' post 1-year treatment scores were descriptively near similar levels respective to their baseline scores – CPAL: N = 9 (21%) vs. N = 6 (21%); DET: N = 10 (23%) vs. N = 7 (24%); IDN: N = 10 (23%) vs. N = 6 (21%) – with the exception of GML: N = 6 (30%) vs. N = 5 (19%) and ONB: N = 6 (14%) vs. N = 6 (21%), which exceeds the normative distribution expectation of 15.9% to be below 1 SD of the mean.

Subject-specific trajectories of Cogstate scores

Figure 3 shows the results of the LCGMM analyses. Our goal was to identify classes of children based on longitudinal patterns of Cogstate scores. Noting the relatively small sample of available participants, growth curve models were optimized in both parsimony and fit within the specification of a two-class model. Based on initial model testing, we included age, sex, risk group, CNS Prophylaxis, irradiation, and median income in patient's zip code as covariates. To determine the appropriate model, we examined the Bayesian (BIC) and Akaike (AIC) information criterion. We sought a model with lower values for the criterion indices. The final model included sex and CNS Prophylaxis group. Figure 3 shows most of the children demonstrated relatively stable trajectory: CPAL (N = 42; 98%), DET (N = 32; 74%), GML (N = 30; 94%), IDN (N = 42; 98%), and ONB (N = 39; 91%).

Discussion

We previously demonstrated the feasibility of using Cogstate to assess baseline neurocognitive functioning during the first month of Induction therapy for childhood ALL at multiple institutions within the DFCI ALL Consortium.[42] This follow up report expands on those findings, demonstrating the feasibility of using the same computer-based battery longitudinal assessment of neurocognitive functioning at repeated timepoints during treatment and one year after completion of planned therapy. The appropriateness of this approach for use in the context of a large multi-institutional clinical trial was illustrated by a high rate of consent/assent by eligible patients and families, as well as high completion rates (88–100%) and performance checks (88–100%) for all subtests. These findings indicate a very high level of tolerance of the cognitive battery and that the tests provided a valid measure of neurocognition.

Consistent with prior reports[12, 13], greather than a third of participants exhibited abnormal neurocognitive functioning over a year after completion of planned chemotherapy, indicated by Cogstate test scores more than 2 standard deviations below age-matched means on at least one subtest. At this time point, all participants have recovered clinically from any acute or subacute toxicity related to chemotherapy (e.g. nausea or fatigue). Any observed neurocognitive deficits are therefore considered a persistent adverse effect of medical treatment for leukemia, consistent with CICI.

Because the purpose of this pilot study was to demonstrate feasibility of longitudinal monitoring of neurocognitive functioning using Cogstate, the study was not powered to identify predictors of persistent neurocognitive deficits. Nevertheless, some interesting patterns were observed through our analysis of changes over time using latent class mixture modeling. The Groton Maze Learning (GML) task appears to be the most sensitive to change over time. Specifically, children between the ages of 5–8 years older showed a greater decline in performance on this task from baseline than those aged 9–19, and girls showed a greater decline than boys. Of note, there was also a trend for females to perform worse over time than males on the CPAL task, which approached statistical

significance. These data suggest that with a larger cohort, analysis using latent class mixed modeling will identify those patients with neurocognitive difficulties early in therapy, when a proactive intervention might prevent further treatment-related neurocognitive impairment.

Our ongoing, prospective study (ClinicalTrials.gov Identifier: NCT03020030) will include longitudinal assessments of cognitive function using Cogstate during treatment and traditional neurocognitive testing one year after completion of chemotherapy. With anticipated accrual of 560 children being treated for leukemia at 8 institutions within the DFCI ALL Consortium, this study is powered to describe the relationship between early changes in neurocognitive function detected by LCMM analysis of Cogstate data and neurocognitive impairment one year off therapy on traditional cognitive assessments. In addition, we will be able to identify predictors of treatment-induced neurocognitive impairment, by studying biomarkers in cerebrospinal fluid indicative of neurotoxicity[44], genetic variants associated with increased susceptibility,[45] and social determinants of health such as household material hardship.[46, 47]

Conclusion

With this pilot study, we demonstrate that Cogstate, a computer battery of cognitive assessments, can be reliably utilized to characterize changes from baseline in neurocognitive functioning during and after treatment for childhood ALL. Applying this approach in a larger, prospective cooperative group trial, we anticipate being able to identify which children with ALL are most susceptible to treatment-induced neurocognitive impairment early during the two years of treatment, when a proactive intervention might prevent this toxic sequela of curative therapy.

Declarations

The work described here was funded in part by the National Institutes of Health, National Cancer Institute, NIH/NCI R21-CA187226.

Availability of data and material:

All raw data will be made available upon request.

Authors' contributions:

- PDC, LBS, and SAS made substantial contributions to the conception and design of the work, supervised the conduct of the project, contributed to analysis and interpretation of the data, drafted the work and revised it critically for important intellectual content.
- SYS, YL, AS, and SR contributed to analysis of the data and prepared figures and tables for the manuscript.
- PDC, KMK, MLS, LMV, and JJW recruited patients for the study.
- All authors reviewed and revised the manuscript critially for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: N/A

Consent to participate:

The institutional review boards of the treating institutions approved the clinical protocols. Informed consent was provided by the subjects' guardians or by those patients over the age of 18 years. Written assent was provided if age-appropriate, following institutional guidelines.

Consent for publication:

All of the material is owned by the authors and/or no permissions are required.

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Tables

Table 1
Timing of Cogstate testing timepoints (designated T1 through T6) and cerebrospinal fluid collection, relative to leukemia therapy phases.

ALL Treatment Phase (Duration)	Cogstate (Time Point, T1-T6)	CSF Collection
Induction (32 days)	One practice plus Baseline, week 4 (T1)	Day 18; Day 32
Consolidation I (3 weeks)	7 weeks post diagnosis (T2)	
CNS Phase (3 weeks)	10 weeks post diagnosis (T3)	At the fourth dose of intrathecal chemotherapy
Consolidation II (30 weeks)	16 weeks post diagnosis (T4)	Week 7 of Consolidation II
Continuation (approx. 70 weeks, until 2 years post remission)	15 months (± 6 weeks) post diagnosis (T5)	15 months (± 6 weeks) post diagnosis
Post-Treatment	1-year (± 8 weeks) post completion (T6)	

Table 2
Baseline Patient Characteristics Presented as N (%)

	N = 43
Age (years)	
5–8	20 (46.5%)
9–19	23 (53.4%)
Sex	
Female	15 (34.9%)
Male	28 (65.1%)
Risk Category[a]	
High Risk	29 (67.4%)
Standard Risk	14 (32.6%)
CNS Prophylaxis	
Intrathecal Chemotherapy	33 (76.7%)
Intrathecal Chemotherapy Plus Cranial Radiation	10 (23.3%)
Median Household Income in Patient's Zip Code	
<= $74,713	21 (51.2%)
> $74, 713	20 (48.8%)

[a]As determined by clinical parameters defined in the treatment protocol.

Table 3
Raw Mean (SD)[1] Cogstate Brief Battery Cognitive Assessments Over Time (N = 43)

	Induction	Consolidation I	CNS Therapy	Consolidation II	Continuation	Post 1-Year Treatment
CPAL	24.02 (24.95)	14.77 (20.48)	18.73 (23.79)	14.81 (20.49)	9.74 (10.72)	16.28 (18.81)
DET	2.59 (0.11)	2.59 (0.11)	2.59 (0.11)	2.6 (0.12)	2.56 (0.13)	2.55 (0.11)
GML[2]	56.66 (17.85)	49.93 (18.43)	49 (19.85)	46.71 (16.66)	50.97 (19.35)	57.38 (29.21)
IDN	2.78 (0.13)	2.78 (0.12)	2.77 (0.13)	2.79 (0.14)	2.75 (0.12)	2.74 (0.1)
ONB	2.93 (0.12)	2.94 (0.14)	2.92 (0.16)	2.92 (0.13)	2.91 (0.12)	2.89 (0.12)

Abbreviation: CPAL, Continuous paired associate learning (errors); DET, Detection (log_{10} milliseconds); GML, Groton maze timed chase test (errors); IDN, Identification (log_{10} milliseconds); ONB, One-back memory (log_{10} milliseconds); IDN, Identification (log_{10} milliseconds); ONB, One-back memory (log_{10} milliseconds).

[1] Lower raw scores indicate better performance.

[2] GML missing data: N = 21 (Induction), N = 15 (Consolidation I), N = 12 (CNS Therapy), N = 11 (Consolidation II), N = 10 (Continuation), N = 2 (Post 1-Year Treatment)

Table 4
Mean Raw Change Score Comparison Across Baseline Characteristics

		Mean Change (CNS Therapy – Induction)[b]					Mean Change (Post-1 Year Treatment – Induction)[b]				
	N	CPAL N = 26	DET N = 26	GML[a] N = 24	IDN N = 26	ONB N = 26	CPAL N = 26	DET N = 26	GML[a] N = 24	IDN N = 26	ONB N = 26
Age (years)											
5–8	10	-6.7 (23.8)	-0.02 (0.07)	4.5 (13.45)	0.03 (0.11)	0.02 (0.1)	-21.6 (26.95)	-0.03 (0.12)	19.50 (19.68)	-0.05 (0.11)	-0.02 (0.15)
9–19	16	-8.12 (14.39)	0.00 (0.05	-15.69 (12.93)	-0.01 (0.06)	-0.02 (0.07)	0.19 (15.85)	-0.03 (0.11)	-9.19 (32.41)	-0.02 (0.09)	-0.07 (0.11)
p-value[c]		0.672	0.487	**0.004**	0.160	0.257	0.102	0.946	**0.014**	0.473	0.333
Sex											
Female	8	2.62 (10.81)	-0.01 (0.07)	0.62 (11.95)	-0.02 (0.09)	-0.01 (0.07)	-12.25 (25.27)	0.00 (0.13)	0.38 (17.66)	-0.03 (0.12)	0.00 (0.09)
Male	18	-12.11 (19.09)	-0.01 (0.05)	-13.75 (16.01)	0.02 (0.08)	0.00 (0.09)	-6.39 (22.45)	-0.05 (0.11)	0.38 (37.12)	-0.04 (0.09)	-0.07 (0.14)
p-value[c]		**0.054**	0.996	**0.024**	0.232	0.978	0.889	0.315	1.00	0.822	0.249
Risk Category											
High Risk	19	-8.84 (19.69)	0.00 (0.05)	-10.33 (16.41)	0.01 (0.08)	-0.01 (0.08)	-5.79 (21.52)	-0.05 (0.08)	0.17 (35.89)	-0.04 (0.09)	-0.06 (0.14)
Standard Risk	7	-4.14 (13.69)	-0.02 (0.07)	-4.83 (15.73)	-0.01 (0.09)	0.02 (0.10)	-14.71 (27.33)	0.01 (0.17)	1.00 (13.78)	-0.03 (0.12)	-0.01 (0.10)
p-value[c]		0.568	0.52	0.480	0.653	0.386	0.772	0.250	0.957	0.794	0.432
CNS Prophylaxis											
Intrathecal Chemotherapy	18	-7.39 (16.34)	-0.01 (0.07)	-10.65 (15.24)	-0.01 (0.09)	0.01 (0.08)	-4.39 (23.37)	-0.02 (0.13)	-1.88 (30.43)	-0.03 (0.09)	-0.05 (0.11)
Intrathecal Chemotherapy Plus Cranial Irradiation	8	-8 (22.93)	0.00 (0.04)	-4.86 (18.55)	0.04 (0.06)	-0.02 (0.09)	-16.75 (21.03)	-0.06 (0.08)	-5.86 (35.91)	-0.05 (0.11)	-0.04 (0.17)
p-value		0.939	0.714	0.435	**0.08**	0.331	0.101	0.490	0.427	0.683	0.559
Median Household Income in Patient's Zip Code											
<= $74,713	14	-12.14 (22.24)	0.00 (0.05)	-11.79 (14.57)	0.00 (0.07)	-0.01 (0.07)	-4.36 (22.23)	0.00 (0.12)	0.86 (35.01)	-0.01 (0.08)	-0.03 (0.12)
> $74, 713	12	-2.25 (10.25)	-0.02 (0.06)	-5 (18.01)	0.01 (0.09)	0.00 (0.01)	-12.67 (24.04)	-12.67 (24.04)	-0.30 (27.71)	-0.06 (0.10)	-0.07 (0.14)
p-value[c]		0.170	0.284	0.319	0.595	0.828	0.157	0.369	0.932	0.178	0.482

[a] N = 2 patients for the GML assessment at Induction, CNS therapy, and/or Post-1 Year Treatment

[b] Negative raw change scores yield improvement; Positive change scores yield deterioration.

[c] Two-sample Wilcoxon/T-tests pending on normality per group level.

Table 5

Cogstate Z-Scores 1 and 2 Standard Deviations or Below the Population Mean Presented As N (%)[a]

	2 or More SD Below the Population Mean							1 or More SD Below the Population Mean		
	Normative[b]	Induction (T1)	Consolidation I (T2)	CNS Therapy (T3)	Consolidation II (T4)	Continuation (T5)	1-Year Post Treatment (T6)	Normative[c]	Induction (T1)	Consolidation I (T2)
		N = 43	N = 32	N = 33	N = 32	N = 32	N = 29		N = 43	N = 32
CPAL[1]	2.3%	4 (9%)	1 (3%)	2 (6%)	1 (3%)	2 (7%)	4 (14%)	15.9%	9 (21%)	1 (3%)
DET		2 (5%)	0 (0%)	1 (3%)	3 (9%)	2 (6%)	5 (17%)		10 (23%)	6 (19%)
GML[2]		1 (5%)	1 (7%)	1 (5%)	0 (0%)	2 (10%)	2 (7%)		6 (30%)	2 (13%)
IDN		3 (7%)	2 (6%)	3 (9%)	3 (9%)	4 (12%)	3 (10%)		10 (23%)	5 (16%)
ONB		1 (2%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)		6 (14%)	4 (13%)

[a] Numbers are counts and percentages unless otherwise noted.

[b] Expected N (%) of z-scores 2 SD or below the norm.

[c] Expected N (%) of z-scores 1 SD or below the norm.

Missing data:

[1] CPAL: N = 21 (Consolidation I, Consolidation II, Continuation),

[2] GML: N = 21 (Induction), N = 15 (Consolidation I), N = 12 (CNS Therapy), N = 11 (Consolidation II), N = 10 (Continuation), N = 2 (Post 1-Year Treatment)

Figures

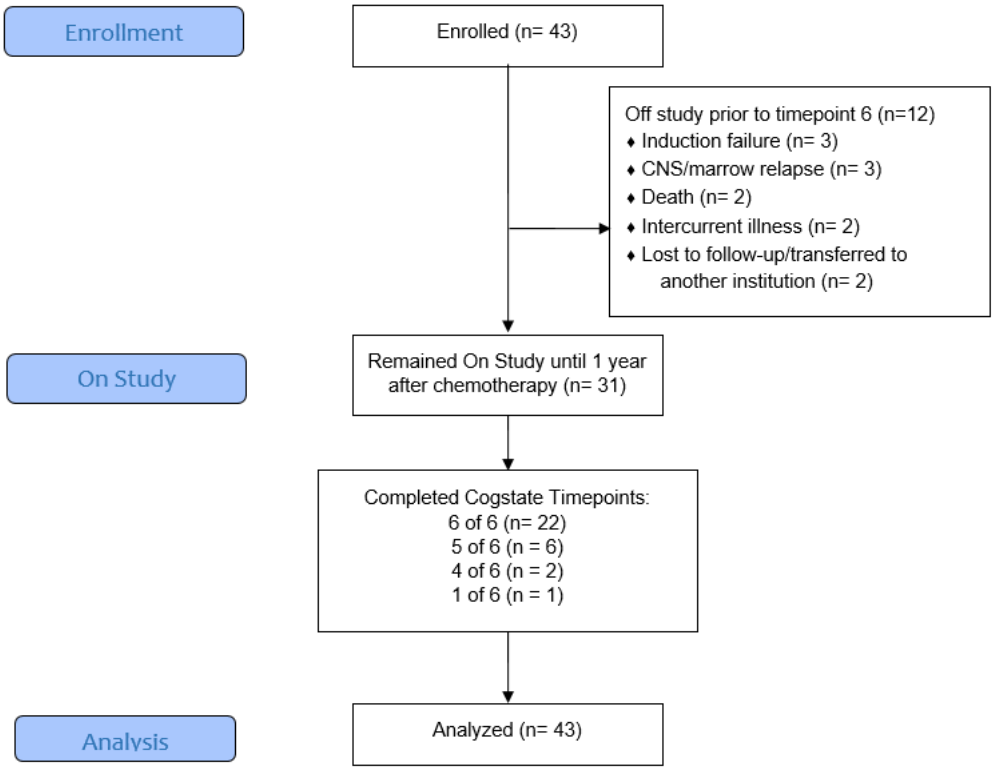

Figure 1

Consort Diagram

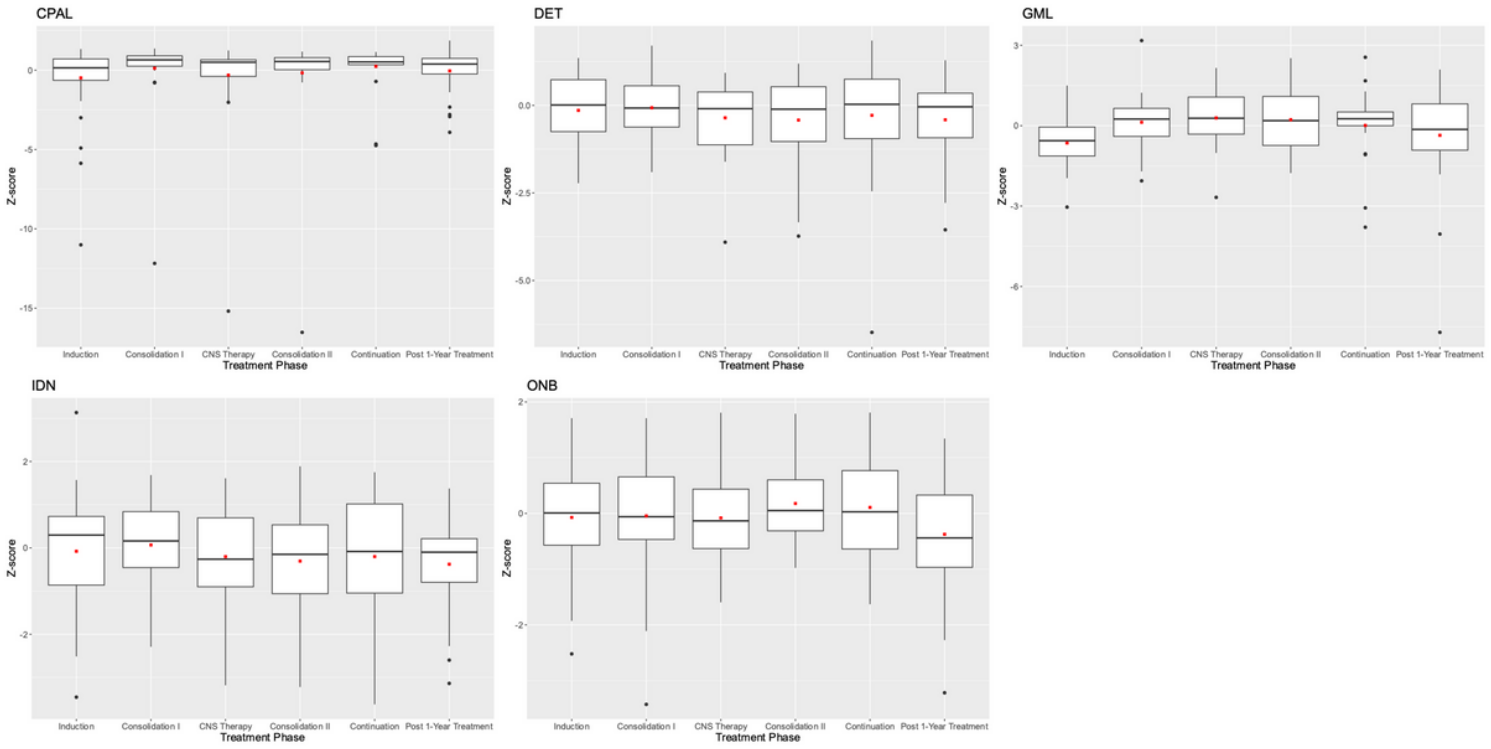

Figure 2

Box and whisker plot of Cogstate Brief Battery Cognitive Assessments Over Time

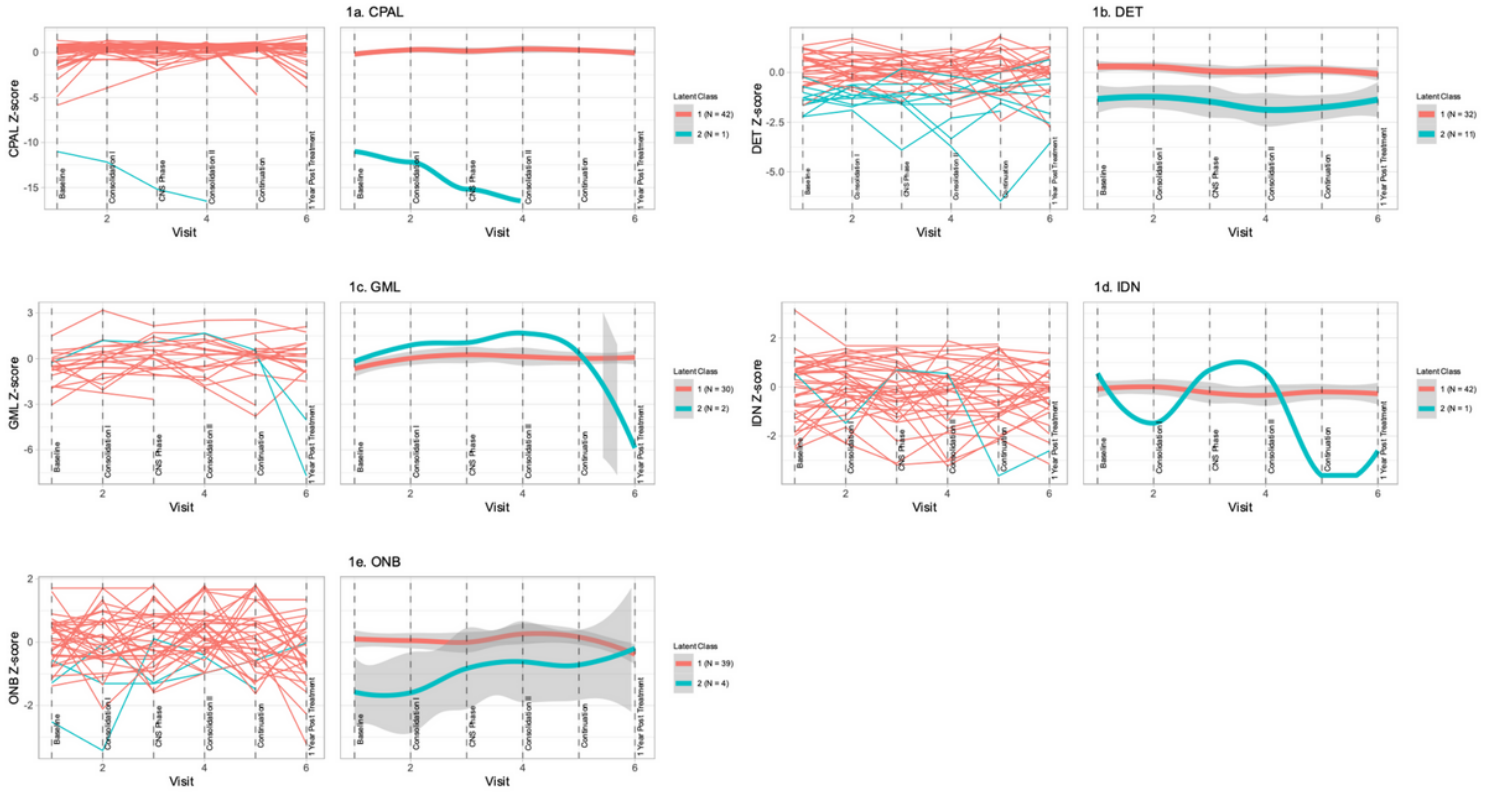

Figure 3

Cogstate Score Trajectories: Estimation of 2 Latent Class Linear Mixed Models

Note.

Dashed lines separate treatment phases.

Majority of patients (red line) perform well across all Cogstate tests.