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Longitudinal analysis of quality of life outcomes in children during treatment for acute lymphoblastic leukemia: a report from the Children's Oncology Group (COG) AALL0932

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Abstract

Background—Children with average-risk acute lymphoblastic leukemia (AR-ALL) face many challenges that can adversely affect quality of life (QOL). However, patterns and predictors of QOL impairment during therapy are not well-characterized.

Methods—AR-ALL patients enrolled on COG AALL0932 were offered participation in this prospective cohort study if 4 years old at diagnosis with an English-speaking parent. At ~2, 8, 17, 26, and 38 (boys only) months after diagnosis, parents completed the PedsQL4.0 and Family Assessment Device instruments for QOL (physical, emotional, and social functioning) and family functioning, respectively. Proportions of individuals scoring in the impaired range (2 SD below population mean) were calculated at each timepoint. Longitudinal impairment patterns and predictors were examined.

Results—594 participants with AR-ALL were diagnosed at a mean age of 6.0(SD:1.6) years. At 2 months, a substantial percentage of participants had impaired scores for physical (36.5%; 95%CI 32.3–40.8) and emotional functioning (26.2%; 95%CI 22.5–30.2) compared to population norms of 2.3%. These elevations persisted at 26 months. Emotional impairment at 2 months (OR 3.4; 95%CI 1.5–7.7) significantly predicted emotional impairment at 26 months. In repeated measures analysis with multivariate modeling, unhealthy family functioning (OR 1.5; 95%CI 1.1–2.1) significantly predicted emotional impairment controlling for age and sex. QOL outcomes were similar between sexes at the end of therapy (girls: 26 months, boys: 38 months).

Conclusions—Many children with AR-ALL experience physical and emotional functioning impairment that begins early in treatment and persists. Early screening may identify high-risk patients who may benefit from family-based interventions.

Keywords

acute lymphoblastic leukemia; health-related quality of life; pediatric; family functioning; emotional functioning

Background

Acute lymphoblastic leukemia (ALL) accounts for approximately 25% of all childhood cancers ¹. With 5-year overall survival rates for ALL approaching and even exceeding 90% in some countries, health-related QOL has emerged as an important measure of successful treatment ². Many of the standard chemotherapy agents used to treat ALL can affect both physical and psychosocial functioning ^{3–5}. Vincristine, methotrexate, and dexamethasone, all common components of ALL treatment regimens, have been linked to peripheral neuropathy, neurocognitive deficits, and increased emotional and behavioral problems respectively ^{6–9}.

Patients with ALL also face disruption to their QOL secondary to infection, unplanned and prolonged hospitalizations, and the fear of potential relapse or death over a treatment period that lasts 2–3 years¹⁰. The frequent hospital visits and need to manage symptoms and painful procedures exact a toll not just on the patients but also on their caretakers¹¹. Compared to parents of healthy children, parents of survivors of childhood leukemia were found to have greater symptoms of post-traumatic stress, with more symptoms associated with poor family functioning¹². Poor or unhealthy family functioning, as defined by various clinical tools and constructs, is marked by high levels of conflict and disorganization, inadequate communication, and emotional dysregulation within the family unit¹³.

In the United States, over 90% of children diagnosed with leukemia each year are treated at a COG member institution¹⁴. Analysis of health-related QOL outcomes on a previous COG ALL clinical trial showed increased frequency of anxiety/depression, and impaired physical and social functioning 2 months after treatment was completed¹⁵. However, these findings were derived from a single study of 160 participants. Unhealthy family functioning was identified as a possible risk factor but required confirmation with a larger sample. In order to inform future screening and interventions to reduce the burden of ALL therapy and improve quality of life for patients and their families, our study aims were to: 1) describe the longitudinal patterns of physical, emotional, and social functioning with standardized instruments during ALL therapy in average risk patients, and 2) identify predictors associated with worse functioning.

Methods

Study Population

This was a prospective cohort study of a subset of children enrolled in the COG interventional clinical trial AALL0932 at 157 COG member institutions. AALL0932 participants were offered this embedded study if they had average risk B-ALL, were 4 years old, had a parent fluent in English, and had no pre-existing neurodevelopmental disorder (i.e. Down syndrome, autism). Average risk B-ALL in this protocol included the subset of National Cancer Institute standard risk patients (initial white blood count <50,000/microliter and age at diagnosis 1.00–9.99 years) who also met the following criteria: no central nervous system (CNS) 3 or testicular leukemia, no Down syndrome, Day 29 bone marrow minimal residual disease (MRD) <0.01%, Day 8 peripheral blood MRD <1% for those with neither favorable nor unfavorable genetics, and Day 8 peripheral blood MRD 0.1% or CNS 2 for those with favorable genetics¹⁶. In total, 594 children were enrolled on this QOL study from centers in the U.S., Canada, New Zealand, and Australia between August 2010 and April 2013. The Yale University Human Investigation Committee and individual institutional review boards of each participating site approved this study. Informed consent and assent, when indicated, were obtained for all participants.

Procedure

Paper surveys for this study were completed by parents at scheduled clinic appointments from early in therapy until the end of therapy: 2, 8, 18, 26, 38 (boys only) months after initial diagnosis. End of therapy is 26 months for girls and 38 months for boys, which

corresponds to 4 evaluations for girls and 5 for boys. Patients with relapse or refractory disease or who withdrew consent for AALL0932 during the course of the study did not complete additional evaluations.

Measures

Measures in this study were based on parent-report. The primary outcome was impairment on the pediatric quality of life inventory 4.0 generic core scales (PedsQL 4.0). The PedsQL 4.0 is a 23-item survey with responses on a 5-point Likert scale that measures a child's quality of life¹⁷. It is reliable and valid in healthy pediatric populations, as well as in pediatric cancer patients^{17–20}. We used a one-month recall period and analyzed subscales for physical, emotional, and social functioning. As in previously published analyses of pediatric cancer patients, impairment was defined as two standard deviations below a healthy population mean^{15, 21}. In terms of missing data, mean subscale imputation was performed if >50% of the items in a domain were answered; otherwise the score was not calculated per the standardized instructions of the author of the scale.

Parents also completed the Family Assessment Device-General Functioning (FAD-GF) subscale at each timepoint to assess family functioning. The FAD-GF consists of 12 questions on a 4-point Likert scale with a validated mean cutoff score of >2.0 for unhealthy family functioning²². It has been shown to be valid and reliable in healthy populations, as well as medical and psychiatric samples^{23, 24}. Scores were not calculated for any surveys missing one or more responses.

Parents completed a baseline demographic and family survey at the first timepoint only, which ascertained race/ethnicity, caregiver education, family income, and family structure.

Statistical Analysis

Participants were compared to non-participants in the larger clinical trial using Kruskal-Wallis test for age at diagnosis, and Fisher's exact tests for sex and race. Participants who completed the final evaluations (26 months for girls, 38 months for boys) were compared to participants who did not using Kruskal-Wallis test for age at diagnosis, and Fisher's exact tests for sex, race, family functioning at 2 months, and impairment on each of the PedsQL subscales at 2 months.

The proportions of participants scoring in an impaired range on the PedsQL, defined as worse than 2 standard deviations below normative means, were calculated for each timepoint for each subscale (physical, emotional, and social functioning). Logistic, univariate regression taking into account repeated measures assessed the relationship between impairment on each subscale and the following independent variables: age at diagnosis, sex, race, Hispanic ethnicity, caregiver's marital status, family income (greater vs. less than \$50,000/year), maternal education, household size (<4 vs. ≥4 people), pregnancy status (pre-term vs. full term), family functioning, any Grade 3 or higher adverse event, any Grade 4 or higher adverse event, any peripheral neuropathy (Grade 3 or higher), febrile neutropenia or infection (Grade 3 or higher). The \$50,000/year cutoff for dichotomizing income was chosen because it most closely aligned with the U.S. median income for families with children between 2010–2013, the years of study enrollment²⁵. Grades 3 and 4 refer to the severity as

set forth by the Common Terminology for Common Adverse Effects 4.0, a standardized classification system that grades adverse effects ²⁶. Grade 3 generally refers to a severe condition vs. Grade 4 which is generally defined as life-threatening ²⁷.

Multivariate modeling, taking into account repeated measures of the outcome at multiple timepoints for each subscale, was then conducted for factors with $p < 0.1$ in the corresponding univariate analysis, as has been convention in other quality of life analyses ^{15, 28}. Fisher's exact tests were performed to compare proportions impaired for each subscale (physical, emotional, social functioning) between boys at 26 months vs. girls at 26 months, as well as between boys and girls at therapy end (38 months and 26 months respectively).

Univariate regression analyses were conducted to test association of impairment on each PedsQL subscale at earlier timepoints (i.e. 2 months, 8 months, 18 months) with impairment at 26 months (i.e. the last timepoint that included data for both boys and girls).

All analyses were conducted using SAS version 9.4.

Results

Participants

Table 1 displays the baseline patient and treatment characteristics of the study sample. A total of 594 children were diagnosed with average risk-ALL at a mean age of 6.0 ± 1.6 years. There were slightly more boys than girls, and the cohort was predominantly white although 16% were Hispanic. A little over half lived in households where the annual income was over \$50,000. The majority of children had caregivers who were married and a mother who had completed some college or higher. Compared to patients with average risk ALL enrolled in AALL0932 who did not participate in this quality of life study, a greater proportion of patients in this analysis were white (68% vs. 55%, $p < 0.01$) and fewer were Hispanic (16% vs. 24%). There was no difference in terms of sex. The completion rates of the PedsQL for each of the timepoints (2 months, 8 months, 18 months, 26 months, and 38 months) were 88% (n=519), 77% (n=344), 75% (n=325), 70% (n=295), and 60% (n=133), respectively (Supplemental Figure). When comparing participants who completed the final evaluation (26 months for girls, 38 months for boys) with those who did not, those who completed the evaluation were more likely to be girls (66% vs. 36%, $p < 0.01$) and less likely to have reported physical impairment on the PedsQL at 2 months (30% vs. 40%, $p = 0.04$). They did not differ in terms of age at diagnosis, sex, family functioning at 2 months, emotional or social impairment at 2 months (all $p > 0.2$).

Rates of Impairment

Figure 1 displays the proportions of patients with impaired scores in physical, emotional, and social functioning across the five timepoints. The expected population norm is 2.3% for proportion impaired on each subscale. At 2 months post-diagnosis, a substantial percentage of the participants had impaired scores for physical (36.5 %; 95% CI 32.3–40.8) and emotional functioning (26.2%; 95% CI 22.5–30.2). Although these proportions improved over time, they remained significantly elevated at 26 months (end of therapy for girls) for physical (11.9%; 95% CI 8.4–16.1) and emotional (9.8%; 95% CI 6.7–13.8) functioning.

These proportions were also elevated for boys at the end of therapy (38 months) (physical functioning 15.0%, 95% CI 9.4–22.3; emotional functioning 8.3%, 95% CI 4.2–14.3). Social functioning impairment was less pronounced and fell within the normal range of the population for all but the first (4.3%; 95% CI 2.7–6.4) and last (boys only; 6.8%; 95% CI 3.1–12.5) timepoints.

Predictors of Impairment

Table 2 lists the associations of patient and family factors with impairment in physical, emotional, and social functioning using repeated measures multivariate logistic regression. Unhealthy family functioning (OR 1.5; 95% CI 1.1–2.1) was significantly associated with emotional impairment controlling for age and sex. Younger age at diagnosis was a significant risk factor for impairment in both emotional (OR 1.2; 95% CI 1.1–1.3) and social (OR 1.4; 95% CI 1.1–1.8) functioning. There were no statistically significant associations found between Grade 3 or higher adverse events (any, neurologic, and infectious) and QOL impairment.

Early impairment predicted later impairment for both physical and emotional functioning (Table 3). Impaired physical functioning at 8 months (OR 6.2; 95% CI 2.5–15.4) and 17 months (OR 11.6; 95% CI 4.8–28.1), though not at 2 months, was predictive of physical functioning impairment at 26 months. Impaired emotional functioning at 2 months (OR 3.4; 95% CI 1.5–7.7), 8 months (OR 3.5; 95% CI 1.4–8.8), and 17 months (OR 16.8; 95% CI 6.5–43.1) predicted emotional functioning impairment at 26 months. However, impaired social functioning at earlier timepoints was not predictive of impairment in social functioning at 26 months (all $p > 0.05$).

Comparison by Sex

Figure 2 displays the proportions of impairment at each timepoint stratified by sex. Compared to boys, girls were more likely to have emotional impairment at 2 months post-diagnosis ($p < 0.01$). Boys were more likely than girls to have physical impairment at 17 months post-diagnosis ($p = 0.04$). Otherwise there were no differences between boys and girls. Notably, at 26 months, there were no statistical differences between boys vs. girls in any of the domains: physical ($p = 0.47$), emotional ($p = 1.00$), or social ($p = 0.34$). At their respective end of therapy timepoints (i.e. 38 months for boys and 26 months for girls), there were similarly no significant differences (all $p > 0.2$).

Discussion

Our longitudinal, prospective analysis of quality of life outcomes in children with ALL demonstrated that many of these patients experience considerable impairment in physical and emotional functioning during treatment. While the proportions of those impaired gradually improved over time, there remained a substantial subgroup of children who continued to exhibit difficulties in physical (11.9%) and emotional (9.8%) functioning even at 26 months post-diagnosis. Our analyses revealed that early impairment predicted later impairment for both physical and emotional functioning and that patients with unhealthy family functioning were 50% more likely to exhibit emotional impairment.

To our knowledge, this is the largest study to date on health-related QOL in children with acute lymphoblastic leukemia, the most common childhood malignancy^{3, 5, 15}. Our analysis benefits from a longitudinal, prospective design that enabled us to characterize patterns and predictors of impairment over the course of treatment. Additionally, the study was open at 157 COG member institutions (80% of all COG institutions with active IRB approval for AALL0932). And while Hispanic patients were underrepresented relative to the larger clinical interventional trial (likely due to study eligibility requirement to have an English-speaking parent), 15.7% of participants were still Hispanic. Diversity in socioeconomic status and maternal education also strengthen the generalizability of these findings. Additionally, it is important to note that the traditional cut-off score on the PedsQL for “at-risk” of QOL impairment is one standard deviation below the population norm as it approximates those of children with severe chronic health conditions (including cancer)^{18, 29}. As in other studies of pediatric cancer patients, we used the more rigorous cutoff of two standard deviations below the population norm to focus on individuals who were particularly vulnerable^{15, 21}.

Similar to our smaller analysis of children with standard risk ALL enrolled in COG AALL0331 between 2005 and 2009, we found that unhealthy family functioning was a significant predictor of impaired emotional functioning¹⁵. This result adds to a broad literature examining the relationships between childhood cancer diagnosis, parental stress, family adjustment, and quality of life^{12, 30–32}. Screening for family functioning can be quick and low-cost; e.g. the instrument we used in this study (FAD-GF) is a short 12-question survey that can be easily administered in clinic²². More importantly, family functioning is potentially modifiable with early intervention, as suggested by a series of promising studies in childhood cancer populations^{33–37}. For example, Kazak et al found that a one-day intervention combining cognitive behavioral therapy and family therapy approaches in adolescent cancer survivors and their parents led to increased cohesion and orderliness³⁷. Other examples of early intervention strategies that have been piloted include a problem-solving skills training for mothers of children newly diagnosed with cancer and a stress management session for parents of bone marrow transplant patients^{33, 38}. Each of these examples employs a targeted family-centered approach to psychosocial needs, underscoring the need for multidisciplinary care and integration of embedded psychologists in the cancer treatment team³⁹.

Our study found that early impairment was a strong predictor of later impairment for physical and emotional functioning. Emotional functioning impairment was predictive starting at 2 months (the first timepoint), while physical functioning impairment was predictive starting at 8 months (the second timepoint). This is a novel result that was not found in the last COG analysis of health-related QOL in ALL patients¹⁵. One of the major differences between the two studies is the timing of the first assessment, which was one month post-diagnosis in the report by Mitchell et al and closer to 2 months post-diagnosis in this study. It is possible that assessment so close to the initial diagnosis at one month does not have predictive value because it still reflects the acute toxicities of induction chemotherapy and/or the initial leukemia presentation. At 2 months after diagnosis, when some patients have potentially experienced improvement in QOL, the impaired population may be more representative of those who will have persistent difficulties later during

therapy. The larger size of the current study (greater than 3 times the earlier sample) also likely provided more power to identify outcome predictors. These results provide a compelling rationale to screen patients for physical and emotional functioning early in therapy to target interventions to patients at the highest risk of later impairment.

The trends in social functioning impairment differed from both physical and emotional functioning. In general, the rates of impairment remained within range of the population norm, with slight increase for both sexes at the end of therapy. A previous study examined children receiving chemotherapy for a heterogeneous group of cancer diagnoses and found that they actually performed better on several dimensions of social functioning compared to a control group of classroom peers⁴⁰. They posited that the cancer experience (i.e. enduring painful procedures, chemotherapy side effects, and the possibility of death) may increase empathy and sensitivity in these patients, leading to better social functioning. They suggested that enduring these challenges when many adults (e.g. parents, teachers, health care team) are providing social support may help build resilience. While our study does not provide the data to explain the phenomenon of a rise in social impairment at the end of therapy, it may be related to a gradual reduction in the involvement of these built-in social support structures as treatment ends. From a developmental perspective, these patients are older at the end of treatment when social demands and expectations are increased⁴¹. It is possible that gaps in social functioning become more apparent with a combination of reduced support and increased demands.

Our analysis was also able to examine sex and age effects on quality of life impairment. Boys with ALL treated on COG clinical trials receive a longer duration of treatment. We did not find any statistical difference in the rates of QOL impairment between boys and girls as analyzed two ways: same elapsed time since diagnosis (at 26 months) and respective end of therapy timepoints (26 months for girls, 38 months for boys). In terms of age effects, children who were diagnosed at younger ages were significantly more likely to exhibit emotional and social impairment. There is a growing body of literature that describes the effects of allostatic load on the developing brain. Non-normative experiences such as illness can induce toxic stress, which causes permanent changes in brain structure and function that alter the child's response to future stressful experiences^{42, 43}. Older children have experienced greater neuronal myelination of their limbic systems, which may mediate symptoms and consequences of early-life stress⁴⁴.

Our findings must be interpreted in light of certain limitations. Response rates dropped to 60 to 70% by the end of therapy. This attrition and missing data is a common problem in large studies of pediatric patients with chronic disease⁴⁵. In comparing participants who completed the final evaluation vs. those who did not, we found that girls and those with better physical functioning at 2 months were more likely to complete the final evaluation. While we do not have the data to know exactly how this non-differential response would affect our findings, it is possible that our study underestimates the actual prevalence of quality of life impairment at the end of therapy given the association between earlier and later physical impairment. Another potential limitation of our study is that all outcomes are based on parent-report which may inaccurately estimate a child's quality of life⁴⁶. However, a structured review of QOL studies in children with ALL noted that children only begin to

give reliable responses around the age of 7 or 8 years, which would have been difficult with our study sample given a median age at diagnosis of 5.7 years and the upper age limit of <10 years for enrollment in this clinical trial ⁵. More importantly, it is recognized that parent-report offers its own valid and complementary perspective on a child's QOL in conjunction with both the pediatric patient and their healthcare providers ⁵.

We conclude from this study that significant proportions of children with ALL experience impaired physical and emotional functioning that begins early in treatment and persists. Our data suggest that patients may benefit from evaluation of QOL as early as 2 months post-diagnosis to identify those at highest risk of later emotional impairment who could be targeted for early intervention strategies. In addition, family functioning is an important modifiable risk factor that may be targeted for early screening and intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Overall proportions of impairments in physical, emotional, and social functioning during ALL treatment. The final timepoint (38 months) only includes boys.

Figure 2. Proportions of impairments stratified by sex during ALL treatment in A) physical functioning, B) emotional functioning, and C) social functioning. Error bars signify 95% CI.

Table 1

Participant characteristics (n = 594) *

Characteristic	n (%)
Sex	
Male	317 (53.4%)
Female	277 (46.6%)
Age at diagnosis in years, mean (SD)	6.0 (1.6)
Race	
White, non-Hispanic	404 (68.0%)
Black, non-Hispanic	25 (4.2%)
Hispanic/Latino	93 (15.7%)
Other or unknown	72 (12.2%)
Annual household income	
<\$50,000	208 (43.2%)
\$50,000	274 (56.8%)
Household size	
4 people	222 (43.9%)
>4 people	284 (56.1%)
Marital status of primary caregiver	
Not married	102 (19.8%)
Married or living together as married	414 (80.2%)
Maternal education	
Less than college	155 (30.4%)
At least some college	354 (69.6%)
Experienced a Grade 3 or higher event during treatment [§]	
Yes	343 (57.7%)
No	251 (42.3%)
Experienced a Grade 4 or higher event during treatment [§]	
Yes	216 (36.4%)
No	378 (63.6%)

* Not all patients had fully completed demographic questionnaires so totals do not always add up to 594.

[§] Only the following toxic events were required reporting for this protocol: CNS hemorrhage requiring medical intervention, GI bleed requiring operative or interventional radiology intervention, pancreatitis requiring medical intervention, osteonecrosis interfering with function, transient ischemic attacks, stroke, encephalopathy, neuropathy (motor or sensory) interfering with ADL, seizure, allergic reaction, ileus, mucositis/stomatitis, bilirubin, thrombosis

Table 2

Associations of patient and family factors[§] with quality of life impairment using repeated measures multivariate logistic regression

	OR (95% CI)	p-value
<i>Physical functioning</i>		
Grade 3 neurologic toxicity	1.6 (1.0 – 2.6)	0.06
<i>Emotional functioning</i>		
Younger age at diagnosis (<5.7 years)	1.2 (1.1 – 1.3)	<0.01 *
Male sex	0.7 (0.5 – 1.1)	0.09
Unhealthy family functioning	1.5 (1.1 – 2.1)	0.02 *
<i>Social functioning</i>		
Younger age at diagnosis (<5.7 years)	1.4 (1.1 – 1.8)	0.01 *

*
p<0.05

[§]Only factors with p<0.1 in univariate analysis were included as part of multivariate modeling for each subscale

Table 3

Associations of earlier quality of life impairment with impairment at 26 months post-diagnosis

	OR (95% CI)	p-value
<i>Physical functioning</i>		
Impairment in physical functioning at 2 months	1.6 (0.8 – 3.2)	0.25
Impairment in physical functioning at 8 months	6.2 (2.5 – 15.4)	<0.01 *
Impairment in physical functioning at 17 months	11.6 (4.8 – 28.1)	<0.01 *
<i>Emotional functioning</i>		
Impairment in emotional functioning at 2 months	3.4 (1.5 – 7.7)	<0.01 *
Impairment in emotional functioning at 8 months	3.5 (1.4 – 8.8)	0.01 *
Impairment in emotional functioning at 17 months	16.8 (6.5 – 43.1)	<0.01 *
<i>Social functioning</i>		
Impairment in social functioning at 2 months	0.8 (0.0 – 15.0)	1.0
Impairment in social functioning at 8 months	5.9 (0.6 – 55.4)	0.20
Impairment in social functioning at 17 months	35.6 (2.0 – 628.5) [§]	0.06

*
p<0.05

[§]OR and 95% CI were obtained from the logistic model using the approximate method. The corresponding approximate p-value was 0.01. All p-values listed in the table were computed using the Fisher's exact test given that it is more accurate than the approximate method when the number of events is smaller.