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A Prospective Study Of Anxiety, Depression, And Behavioral Changes In Children With Acute Lymphoblastic Leukemia

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A PROSPECTIVE STUDY OF ANXIETY, DEPRESSION, AND BEHAVIORAL CHANGES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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A PROSPECTIVE STUDY OF ANXIETY, DEPRESSION, AND BEHAVIORAL CHANGES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Over 90% of children with standard risk-acute lymphoblastic leukemia (SR-ALL) will survive, but there are limited data concerning their psychological adjustment during treatment. We prospectively assessed symptoms of anxiety, depression and behavioral disturbances in children with SR-ALL during the first 12 months of therapy and identified factors associated with psychological distress. We conducted a cohort study of 159 children 2-9.99 years old with SR-ALL enrolled and treated on Children's Oncology Group study AALL0331 at 31 selected sites. The primary caregiver completed the Behavior Assessment System for Children-Second Edition, the Family Assessment Device-General Functioning, and the Coping Health Inventory for Parents at about 1, 6 and 12 months after starting treatment. The mean scores for anxiety, depression, aggression and hyperactivity in the child were within the average range at all timepoints. However, compared to a normative population, a higher percentage of children scored in the *at-risk/clinical range* for depression throughout the first year: one month (21.7% vs. 15%, $p=0.022$), six months (28.6% vs. 15%, $p<0.001$), and twelve months (21.1% vs. 15%, $p=0.032$). For anxiety, a greater percentage scored in the *at-risk/clinical range* at one month (25.2% vs. 15%, $p=0.001$), but then reverted to expected levels at six and

twelve months after diagnosis. Children with elevated anxiety symptoms at one month were more likely to have elevated symptoms at six (OR=7.70, $p<0.001$) and twelve months (OR=7.11, $p=0.002$) after diagnosis. Similarly, those with elevated depression symptoms at one month were more likely to have elevated symptoms at six (OR=3.51, $p=0.015$) and twelve months (OR=3.31, $p=0.023$) after diagnosis. In multivariate longitudinal analysis with repeated measures at the three timepoints, unhealthy family functioning was associated with anxiety (OR=2.24, $p=0.033$) and depression (OR=2.40, $p=0.008$). Hispanic ethnicity was also associated with anxiety (OR=3.35, $p=0.009$). Worse physical functioning ($p=0.049$), unmarried parents ($p=0.017$), and less reliance on the coping strategy of maintaining social support ($p=0.004$) were associated with depression. Based upon parental assessments, anxiety is a significant problem in young children with ALL one month after starting therapy, though it resolves within the first year. Depression remains a significant problem for at least one year, highlighting the need for psychosocial screening and the availability of mental health staff. We found that we could identify children at one month after diagnosis who were substantially more likely to have poor emotional functioning throughout the first year of therapy. Children of Hispanic ethnicity or from families reporting unhealthy family functioning may be particularly vulnerable.

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INTRODUCTION

Background and Significance

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children, comprising 25% of malignancies diagnosed before age 15 years and 19% diagnosed before age 20 years (1). Its peak incidence is between 2 and 5 years old (2). Children can present, often insidiously, with various constellations of signs and symptoms. Bone marrow infiltration of leukemic cells can lead to signs of bone marrow failure, including fevers (neutropenia), fatigue (anemia), petechiae, and bleeding/bruising (thrombocytopenia). Extramedullary disease can present with lymphadenopathy and hepatosplenomegaly (2). A definitive diagnosis is established with a bone marrow examination. The leukemic cells represent a clonal expansion of cells that originated either from the B- or T-cell lineages. The most common immunophenotype is precursor B-cell ALL (3).

In the 1960s, the five-year survival rate of childhood ALL was less than 10% (4). During subsequent decades, survival rates improved substantially. For United States patients, five-year survival increased to 77% in 1985-1994, to 87% in 1995-2000, and to over 90% in 2000-2005 (1). In particular, children diagnosed with standard-risk ALL and treated on a Children's Oncology Group (COG) clinical trial between 2000 and 2005 had a 95% survival rate (1).

The improved survival rate is, in part, due to more aggressive treatment protocols administered over 2½ to 3½ years (5). Contemporary ALL treatment regimens generally

consist of three main phases: induction of remission, consolidation/intensification with reinduction segments, and prolonged continuation/maintenance (6). In each phase, combination chemotherapy is delivered primarily in the outpatient setting. In addition, patients receive central nervous system prophylaxis with intrathecal medications. Some patients also receive cranial radiation. At diagnosis, patients are classified as standard-risk or high-risk based on age and initial white blood cell count. National Cancer Institute criteria for standard-risk ALL include white blood cell count <50,000/microliter and age 1.0-9.99 years (7). There are additional risk stratifications and specific protocols tailored to immunophenotype and risk status (6).

Since the vast majority of children treated for ALL are expected to become long term survivors, more attention has been devoted to understanding patients' quality of life. In 1998, the American Cancer Society Task Force on Children and Cancer stated: "The progress achieved in attaining 80% survival among children and young adults with cancer can be justified only if their physical, emotional and social quality of life are also protected" (8). We know that the multiple different chemotherapeutic agents used to treat ALL have the potential to affect mood and behavior. In particular, corticosteroids, which are a key component of ALL therapy, affect mood, behavior, and cognition (9). In addition, the 2½ - 3½ years of frequent outpatient visits and unscheduled hospital admissions for complications can take an emotional toll on patients and families. Therefore, it is important to understand the psychological status of ALL patients and make sure their psychosocial needs are fulfilled.

Psychological Health of Childhood Cancer Survivors

Information about the behavioral and emotional health of children with cancer is largely based on studies of children after therapy, rather than children on active treatment (10). In 1981, Drs. Koocher and O'Malley published the results of their landmark study of the psychosocial consequences of surviving childhood cancer (11). The study, which began in 1975, was the first to assess a sizeable group of childhood cancer survivors and their families using standardized instruments in conjunction with clinical interviews. Of the 117 survivors in their cohort, the majority were doing well, but approximately 25% were rated as having impaired psychological adjustment. The prognosis of childhood cancer has improved dramatically since Drs. Koocher and O'Malley's work and a vast amount of literature regarding psychosocial adjustment of survivors has accumulated.

A substantial portion of the literature regarding the psychological status of survivors reported data from the Childhood Cancer Survivor Study (CCSS). The CCSS is a retrospective cohort of over 14,000 childhood cancer survivors and their siblings from 26 institutions in the United States who were diagnosed with cancer between 1970 and 1986 (12). Taken together, results of the CCSS and other childhood cancer survivor studies indicate that most survivors have few emotional and behavioral problems; however, a subset of patients experience significant psychological distress (13, 14). For instance, in a study of 9,535 survivors and 2,916 siblings from the CCSS cohort, survivors were more likely than their siblings to report clinical levels of emotional distress (OR=2.2; 95% CI, 1.8-2.8) and impairments in mental health (OR=1.8; 95% CI, 1.6-2.1) (15).

The data on leukemia patients has yielded similar results. In another CCSS analysis, the 2,090 survivors of ALL reported more symptoms of anxiety (mean score: 47.62 vs. 46.36, $p<0.003$) and global distress (mean score: 48.84 vs. 46.64, $p<0.003$) than their siblings (16). The effects sizes, however, were small and mean scores for both the survivor and sibling participants were below population norms. Likewise, a subset of 1,345 adolescent survivors of leukemia in the CCSS cohort had higher rates of anxiety/depression (OR=1.6; 99% CI, 1.2-2.2) and antisocial behavior (OR=1.7; 99% CI, 1.3-2.3) than their siblings (17). In trying to determine which subsets of patients are particularly vulnerable, a number of variables have been studied. Factors that have been associated with psychological distress in survivors include exposure to more intensive chemotherapy, poor physical health, female sex, unmarried status, and lower annual household income (14, 16, 17). In addition, there is evidence that emotional distress in survivors is related to engagement in risky health behaviors, such as smoking and heavy alcohol use (14, 18).

Cross-Sectional Data on Children on Active Treatment for ALL

Less research about psychosocial outcomes has focused on the active treatment period. Overall, the available literature indicates that children on treatment have poorer emotional and behavioral health compared with childhood cancer survivors (19). The data available on children undergoing treatment for ALL, however, has come from cross-sectional studies that yielded mixed results (20-22). The largest study of this nature, by Sung and colleagues, evaluated 206 children ages 2-18 years with standard-risk and high-risk ALL at five pediatric cancer centers in Canada (20). The patients were at various

points in therapy, but all had been diagnosed at least two months prior to enrollment in the study. On the Pediatric Quality of Life Inventory (PedsQL), the patients had median psychosocial summary and emotional functioning scores that were 1-2 standard deviations lower than healthy population norms. However, differences were not detected between participants in different phases of therapy. Children who were on phases preceding Maintenance had similar emotional (60.0 vs. 65.0, $p=0.087$) and psychosocial (66.7 vs. 58.3, $p=0.152$) summary scores to children on Maintenance. Similarly, in a study of 31 ALL patients on Maintenance therapy, Waters and colleagues found that ALL patients had significantly poorer behavioral and emotional health than a healthy population (22). On the Child Health Questionnaire (CHQ), the 5-17 year old patients had a mean emotional/behavioral health scale score of 80.90 compared to 93.73 in a representative, healthy population ($p<0.001$).

In contrast, in a study by Shankar and colleagues, the 46 children on treatment for leukemia had similar psychological functioning to 481 healthy controls (21). This study of children 8-12 years old utilized the child self-report Minneapolis-Manchester Quality of Life-Youth Form (MMQL-YF). Mean psychological functioning scores were 3.93 and 3.82 for the leukemia patients and controls, respectively ($p=0.17$). Since this data is all cross-sectional, the developmental trajectory of the psychosocial adjustment of ALL patients throughout therapy cannot be determined. Furthermore, it is not clear if the measurement of children at disparate times of treatment contributed to the inconsistencies among various study results.

Longitudinal Data on Children on Active Treatment for Cancer

The few longitudinal studies of psychological adjustment in children on treatment for cancer were small and included diverse cancer populations (23). For example, Landolt and colleagues assessed a cohort of 52 patients in Switzerland at 6 weeks and 1 year after the diagnosis of leukemia, lymphoma, brain tumors or other solid tumors (24). On the TNO-AZL Questionnaire for Children's Health-Related Quality of Life (TACQOL), the 6.5-15 year old children reported significantly worse positive emotional functioning than the community sample at six weeks (mean scores: 5.9 vs. 7.2, $p<0.001$) after diagnosis. Mean scores improved from the first to second timepoint (5.9 vs. 6.6, $p<0.05$); however, at one year after diagnosis, mean scores were still significantly reduced compared to the community sample (6.6 vs. 7.2, $p<0.01$). The other measure of psychological functioning in this study, negative emotional functioning, was not increased in patients. Only 17 patients in the sample had a diagnosis of leukemia. Therefore, it was difficult to ascertain if there were differences in leukemia patients' emotional functioning compared to patients with other diagnoses.

In a series of two longitudinal studies that yielded some dissimilar results to Landolt and colleagues' study, Sawyer and colleagues evaluated a cohort of 39 patients immediately after diagnosis and then annually for the next four years (23, 25). Compared to a community sample of 49 children in South Australia, the patients, who were 2-12 years old at diagnosis, had worse psychological adjustment immediately after diagnosis. Mean scores on two scales of the Child Behavioral Checklist (CBCL) were increased in the patients (higher scores indicate more problems): Total Problems (54.5 vs. 51.0, $p<0.05$)

and Internalizing Problems (56.2 vs. 50.7, p=0.006). Similarly to Landolt and colleagues' study, patients' scores on the Internalizing Problems scale improved across time ($F(4,190) = 2.8$, $p = 0.03$). Unlike the Landolt and colleagues study, however, by one year after the initial assessment, all CBCL scale scores were similar between the patient and community groups. The scores remained similar at all subsequent assessments. Externalizing Problems were not a significant issue at any timepoint. Again, Sawyer and colleagues' study included children with Wilms Tumor, Hodgkin's Lymphoma, and other cancers in addition to leukemia. While 56% of the sample had a diagnosis of ALL, data from the ALL population was not analyzed separately.

Determinants of Psychological Health

The literature has also been inconsistent regarding determinants of psychosocial functioning (19, 26). Many of the aforementioned studies indicate that there are vulnerable subgroups of children who experience greater psychological distress, but there is disagreement about which groups are vulnerable. In a systematic review of predictors of quality of life in children with cancer and childhood cancer survivors, Klassen and colleagues identified a large number of variables (19). Yet, most of the variables in the 58 articles reviewed were examined in only a few studies. Furthermore, they were often significant in one study, but not replicated by the others. For example, lower socioeconomic status was associated with worse emotional functioning in a cross-sectional study of 376 children on active treatment for cancer (OR=1.77; 95% CI, 1.00-3.12) (27). Conversely, in another 6 studies that explored the relationship between socioeconomic status and quality of life, no association was found (19). The few factors

that were consistently related to quality of life included certain cancer variables (e.g., type of cancer), treatment variables (e.g. treatment intensity), and treatment-related (e.g. presence of late effects) variables.

An inspection of more specific studies that included significant samples of children on treatment for ALL indicates that several child and family factors may also be associated with psychological functioning. Both younger and older age at diagnosis or assessment predicted worse emotional and behavioral functioning in different studies (20, 24, 28, 29). For instance, in a cross-sectional study of 215 children (24.2% with leukemia) in Egypt, older age at assessment was related to better emotional functioning (β=0.15, $p<0.01$) (29). In contrast, Sung and colleagues' study of 206 children with ALL (reviewed above) observed that older children had worse psychosocial summary scores on the PedsQL (β= -0.72, p=0.02) (20). There is also data showing an association between female gender and worse emotional health (20, 30). In a cohort study of 101 children (33% with ALL) in Sweden, boys had higher mean "Emotions" scores than girls 2.5 months (62.2 vs. 49.4, $p<0.01$) and 5 months (67.4 vs. 52.6, $p<0.01$) after the start of treatment (30).

In addition to child factors, several family factors have been associated with worse psychosocial functioning in children, including parental health and well-being and unmarried parents. In a study of 87 families (63% with ALL), mothers who had worse scores on the maternal worry scale rated their child's emotional functioning to be lower (r= -0.36, $p<0.05$) (31). Similar correlations were demonstrated in other studies that

measured different aspects of parental distress including anxiety and depression (32-34). Married parents were associated with better emotional functioning in Sung and colleagues' report (β=9.66, p=0.009) (20). Again, most of this literature reviewed did not separately analyze ALL patients. Thus, it is unknown which variables are the most important determinants of psychological functioning in children with ALL.

Role of Family Functioning and Coping Behaviors

The contribution of family functioning and coping behaviors to children's emotional functioning is of particular interest because there are emerging data that suggest these factors may be modifiable. Currently, there is compelling evidence for the efficacy of family interventions in non-cancer childhood illness populations, such as in Diabetes Mellitus (35). Armour and colleagues conducted a meta-analysis of eight randomized controlled trials that evaluated the effectiveness of family interventions in families of children with Type 1 diabetes (36). This meta-analysis revealed an overall decrease in Hemoglobin A1C (HbA1C) levels in children whose families were in the intervention versus control groups. The pooled effect size for HbA1C changes was -0.6% (95% CI, -1.2, 0.1). In addition, five of the six studies analyzed demonstrated a significant improvement in family conflict. However, this could not be quantified in the meta-analysis because of differences in family climate measures between studies (36). Similar published evidence is available for family interventions for children with obesity and cystic fibrosis (35, 37, 38).

The evidence for family interventions in pediatric cancer populations is less certain; however, data from a few small studies are supportive. For example, Kazak and colleagues found that a family-based intervention for adolescent survivors of childhood cancer and their families improved symptoms of posttraumatic stress (39). Kazak and colleagues conducted a randomized clinical trial of the Surviving Cancer Competently Intervention, a four-session, one-day whole family intervention that integrates cognitive-behavioral treatment with family therapy. Of the 150 families who participated, the adolescent survivors in the intervention group improved more on symptoms of arousal than did those in the wait-list control group, $t(20) = 3.13$, $p < .01$. In addition, there was a greater reduction in symptoms of intrusion in the fathers in the intervention versus control group, $t(116) = 3.08$, $p < .01$ (39). Though several of posttraumatic stress and anxiety outcomes did not change with the intervention, Kazak and colleagues' data supported the usefulness of brief family-based treatments in childhood cancer.

Limitations of Previous Research and Their Implications for Future Research

The extant literature on the psychological adjustment of children with cancer has been limited by small sample sizes, diverse patient populations, and cross-sectional designs. In addition, many of the studies reviewed above utilized instruments that may not be the most appropriate measures of psychological adjustment in childhood cancer populations. The use of the Child Behavioral Checklist (CBCL) in children with chronic illnesses, for example, has been cautioned against because of: (1) the confounding of somatization symptoms with the physical symptoms of illness/therapy; and (2) because of inadequate

sensitivity to detect subclinical levels of psychological problems (40). These study design limitations may, in part, account for the inconsistencies in outcomes of prior research.

Two systematic reviews of quality of life in children with ALL are available (10, 26). Both concluded that there is a need for ongoing research that uses longitudinal designs and larger sample sizes to study childhood ALL patients' quality of life. Yet, no study to date has assessed the prospective, longitudinal psychological functioning of children undergoing contemporary therapy for standard risk-ALL (20).

STATEMENT OF PURPOSE, HYPOTHESES, AND SPECIFIC AIMS

We prospectively evaluated the emotional and behavioral functioning of a large, representative sample of children with acute lymphoblastic leukemia enrolled on a frontline Children's Oncology Group (COG) therapeutic study during the first year of therapy. We sought to:

(1) Describe the longitudinal trajectory of the psychological adjustment of children during their first year of therapy by measuring symptoms of anxiety, depression and behavioral disturbances at three select timepoints.

(2) Identify factors associated with worse psychological functioning in children, including potentially modifiable variables related to family functioning and coping that could be targeted in future interventions.

We hypothesized that:

(1) Children with ALL would be at increased risk for poor psychological adjustment in the immediate post-diagnosis period. Psychosocial functioning would then improve; however, a subset of children would have persistently poor emotional and behavioral health throughout the first year of therapy.

(2) Predictors of elevated symptoms of anxiety, depression and behavioral problems would include: older age at diagnosis, female gender, unhealthy family functioning, lack of family coping behaviors, and unmarried parents.

METHODS

Study Population

We conducted a prospective, longitudinal study of emotional and behavioral outcomes in children with standard risk acute lymphoblastic leukemia (SR-ALL) who were enrolled on COG protocol AALL0331 between April 2005 and March 2009 at 31 selected sites. For the AALL0331 therapeutic study, the population of patients with National Cancer Institute standard risk features by age (1.0-9.99 years) and white count (initial white blood cell count <50,000/microliter) were further risk stratified into *standard risk-low*, *standard risk-average*, and *standard risk-high* groups as detailed at trials.gov AALL0331 (7, 41). For this study of emotional and behavioral outcomes, we included children in the *standard risk-average* group, who generally met the following additional criteria: 1) No central nervous system disease (white blood cells in cerebrospinal fluid <5/microliter); 2) No testicular leukemia (no testiculomegaly); 3) A rapid early response to therapy based on bone marrow morphology at day 8/15 of induction therapy and bone marrow minimal residual disease burden at the end of induction; and 4) No unfavorable cytogenetic features (e.g. no triple trisomies or TEL-AML1) (42).

Additional eligibility requirements included age ≥ 2 years and at least one parent with reading comprehension of English or Spanish, the languages for which validated surveys exist. The sites that participated in this study were chosen from all COG sites to include a combination of community-based and tertiary care centers with available staffing to administer the additional surveys for this ancillary study. Participating sites are listed in Table 1.

Table 1. List of participating institutions

Children's Hospital Medical Center, Akron, OH
Children's Hospital at the Cleveland Clinic, Cleveland, OH
Children's Hospital Colorado, Aurora, CO
Children's Hospital of Central California, Madera, CA
Children's Hospital and Clinics of Minnesota, Minneapolis and St. Paul, MN
Children's Hospital, New Orleans, LA
Children's Hospital of Pittsburgh, Pittsburgh, PA
Seattle Children's Hospital, Seattle, WA
Helen DeVos Children's Hospital, Grand Rapids, MI
Doernbecher Children's Hospital, Portland, OR
Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE
East Tennessee Children's Hospital, Knoxville, TN
Hackensack University Medical Center, Hackensack, NJ
Randall Children's Hospital at Legacy Emanuel, Portland, OR
Loma Linda University Medical Center, Loma Linda, CA
Midwest Children's Cancer Center, Milwaukee, WI
Nevada Cancer Research Foundation
Princess Margaret Hospital for Children, Perth, Australia
St. Vincent Hospital, Regional Cancer Center, Green Bay, WI
Packard Children's Hospital at Stanford, Stanford, CA
SUNY Upstate Medical University, Syracuse, NY
St. Joseph's Children's Hospital of Tampa, Tampa, FL
University of Alabama at Birmingham Hospital, Birmingham, Al
University of Florida Academic Health Center, Gainesville, FL
University of Minnesota Medical Center, Fairview, Minneapolis, MN
Children's Hospital, University of Mississippi Medical Center, Jackson, Mississippi
University of New Mexico Children's Hospital, Albuquerque, New Mexico
University of Texas Southwestern Medical Center, Dallas, TX
American Family Children's Hospital, University of Wisconsin Children's Hospital, Madison, WI
Children's Hospital at Vanderbilt, Nashville, TN

The treatment phases in the AALL0331 protocol included Induction (35 days), Consolidation (29-57 days), Interim Maintenance (57 days), Delayed Intensification (57 days), and Maintenance (2-3 years). Patients received a three-drug, four-week induction with vincristine, PEG-asparaginase, dexamethasone (6 mg/m^2/day x 28 days) and intrathecal chemotherapy. No patients received cranial radiation. There were two therapeutic randomizations: (1) a standard Consolidation phase vs. an intensified Consolidation phase and (2) standard Interim Maintenance and Delayed Intensification phases vs. augmented Interim Maintenance and Delayed Intensification phases. In 2008, the second randomization was halted based upon the results of the CCG 1991 SR-ALL

trial (5). Detecting differences in emotional and behavioral functioning between the four treatment groups was not an objective of the current study. However, we were able to analyze if there was an effect of treatment group on psychosocial functioning.

One hundred ninety four patients who were enrolled in AALL0331 at the participating sites met the eligibility criteria for this ancillary study. Of these, 24 declined and 170 consented to participate. Of those who consented, 4 withdrew from AALL0331 before the first required survey evaluations and 7 were not given the evaluations because of error at the study sites (Figure 1). The 159 participants (82% of eligible) were similar to the 35 eligible nonparticipants in terms of age at diagnosis and gender, but there were some differences in ethnicity (Table 2).

Figure 1. Participant flowchart

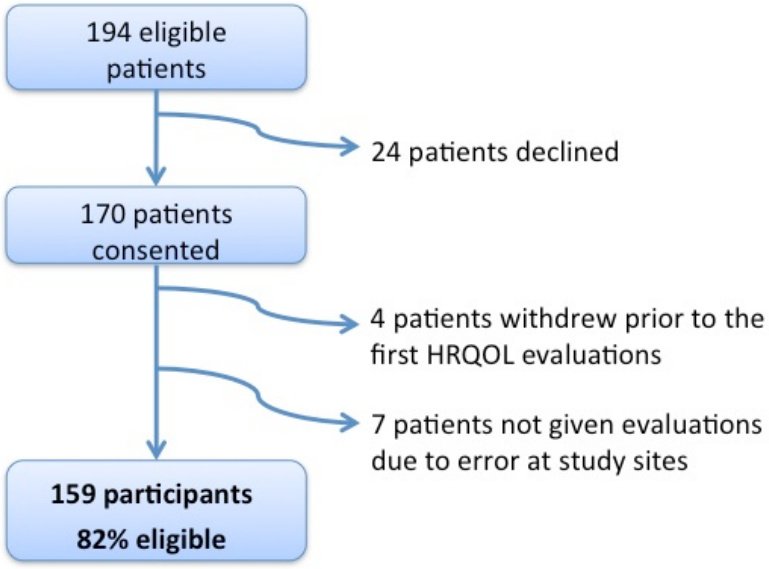


Table 2. Comparison of participants to eligible nonparticipants

	Participants, (n = 159)	Eligible nonparticipants, (n = 35)	P-value
Age group at diagnosis, no. (%)			
Pre-school (ages 2-4)	86 (54.1%)	24 (68.6%)	0.134
School-age (ages 5-9)	73 (45.9%)	11 (31.4%)	
Sex, no. (%)			
Female	76 (47.8%)	19 (54.3%)	0.576
Male	83 (52.2%)	16 (45.7%)	
Child ethnicity, no. (%)			
White, non-Hispanic	108 (67.9%)	16 (45.7%)	0.011
Black, non-Hispanic	11 (6.9%)	1 (2.9%)	
Hispanic	26 (16.4%)	9 (25.7%)	
Other	14 (8.8%)	9 (25.7%)	
Marital status of parents, no. (%)			
Married	105 (66.0%)		
Not Married	45 (28.3%)		
Missing	9 (5.7%)		
Maternal highest level of education, no. (%)			
Less than college	92 (57.9%)		
At least some college	55 (34.6%)		
Missing	9 (5.7%)		
Family Income, no. (%)			
Less than $50,000	72 (45.3%)		
$50,000-$79,999	25 (15.7%)		
$80,000 or more	30 (18.9%)		
Missing	32 (20.1%)		
Therapeutic randomization, no. (%)			
Standard CS/standard IM-DI[1]	42 (26.42%)		
Intensified CS/standard IM-DI[1]	51 (32.08%)		
Standard CS/augmented IM-DI[1]	37 (23.27%)		
Intensified CS/augmented IM-DI[1]	29 (18.24%)		

[1]CS = consolidation, IM = Interim Maintenance, DI= Delayed Intensification

Procedures

The institutional review board of each participating center as well as the Yale University Human Investigation Committee approved the current study. Eligible patients were asked to participate at the end of Induction and were approached for consent at the same time that they were approached for consent to the post-Induction portion of the therapeutic study. Informed consent and assent, when indicated, was obtained for all participants.

The identified primary caregiver (the child's mother in 84% of instances), who accompanied the child to clinic visits, completed surveys at three selected timepoints during their child's first year of therapy: day 1 of Consolidation (approximately 1 month after diagnosis), the end of Delayed Intensification (approximately 6 months after diagnosis), and six months after starting Maintenance (approximately 12 months after diagnosis). The timepoints were chosen to reflect the children's experiences at different phases of therapy. The first represented the induction experience, the second represented the delayed intensification experience, and the third reflected the children's psychosocial functioning mid-Maintenance. Of the 159 participants, 145 completed the evaluations at the first timepoint, 131 completed the evaluations at the second timepoint, and 136 completed the evaluations at the third timepoint.

Measures

Emotional and behavioral functioning was assessed by the Behavioral Assessment System for Children, Second Edition: Parent Report Scale (BASC-2 PRS), a valid and reliable instrument that has been used successfully in pediatric oncology populations (40, 43). The BASC-2 PRS, which has separate forms for parents of pre-school (ages 2-5 years) and school-age (ages 6-11 years) children, contains 134-160 items. The instrument takes 10-20 minutes to complete and there are both English and Spanish versions. Parents rate the frequency of their child's behavior on a 4-point Likert scale ranging from "never" to "almost always." Example items include: *"cries easily, listens to directions, gets very upset when things are lost,* and *acts out of control."* The BASC-2 PRS yields standardized T-scores ranging from 0-100 on a variety of clinical scales. T-scores from

60 through 69 represent the *at-risk* range and scores of 70 and above represent the *clinical significant* range. The BASC-2 PRS has been standardized on *normative* data obtained from a random sample of 12,350 children who are representative of the United States population based on gender, ethnicity, socioeconomic status, geographic region and culture (44). Expected frequencies of scores in the *at-risk* and *clinically significant* ranges in the normative (i.e. healthy comparison) population of children are available in the BASC manual (43). For the current study, the hyperactivity, aggression, anxiety and depression scales were selected because these are the problems known to be associated with steroids and observed in ALL patients. In addition, we did not include the somatization scale because the items are confounded by physical toxicities of therapy. Since the somatization scale is part of the internalizing problems composite scale, we also did not analyze the composite scale.

Family functioning was evaluated using the General Functioning Scale of the Family Assessment Device (FAD-GF), which is appropriate for use in families experiencing chronic illnesses (45, 46). In this 12-item questionnaire, parents use a 4-point Likert scale ranging from "strongly disagree" to "strongly agree" to indicate the degree to which they feel each statement describes their family. Example items include *"we are able to make decisions about how to solve problems," "we cannot talk to each other about the sadness we feel,"* and "*we feel accepted for what we are."* The possible scores range from 1-4, with higher scores reflecting greater perceived family dysfunction. A cut-off point for the FAD-GF has also been established; scores <2 signify healthy family functioning and scores ≥ 2 signify unhealthy family functioning (46).

Family coping was assessed using the Coping Health Inventory for Parents (CHIP), which has been validated for children with a variety of chronic illnesses (47). In this 45-item checklist, parents rate how useful a specific coping behavior is on a 4-point Likert scale ranging from "not helpful" to "extremely helpful." The CHIP has three subscales developed through factor analysis: (1) Maintaining Family Integration and Optimism (e.g. *"Doing things together as a family,"* 19 items, maximum score: 57); (2) Maintaining Social support and Self-Esteem (e.g. *"Explaining our family situation to friends and neighbors so they will understand,"* 18 items, maximum score: 54); and (3) Understanding the Medical Situation (e.g. *"Reading about how other persons in my situation handle things,"* 8 items, maximum score = 24). The coping patterns have α-reliabilities of .79, .79, and .71, respectively (48). A higher score on each of the three subscales denotes a greater reliance on that particular coping pattern, but there are no normative scores.

Physical functioning was measured with the "pain and hurt" and "nausea" subscales of the Pediatric Quality of Life Inventory (PedsQL) 3.0 Cancer Module. The PedsQL Cancer Module is a reliable and valid cancer-specific instrument (49). Parents rate how much of a problem each symptom has been during the past month on a 5-point Likert scale ranging from "never a problem" to "almost always a problem." The "pain and hurt" *(e.g. "aches in joints and/or muscles")* and "nausea" *(e.g. "feeling too nauseous to eat")* subscales contain two and five items, respectively. Scores are reverse-scored and transformed on a 0-100 scale, with higher scores signifying better physical functioning.

Socioeconomic data were obtained at the first timepoint from a parent demographic survey, which included questions about ethnicity, household income, marital status, maternal education and family size.

Data Analysis

Patient characteristics, including age at diagnosis, gender, and ethnicity, were summarized and compared between participants and eligible nonparticipants using an exact chi-square test to evaluate the potential for response bias.

The primary outcomes of interest were the BASC-2 subscales for anxiety and depression. A patient was considered in the *at-risk/clinically significant* range if the corresponding subscale score was ≥ 60 and in the *clinically significant* if the score was ≥ 70, consistent with how this instrument was validated. The proportions of patients in the *at-risk/clinically significant* and *clinically significant* ranges were compared to the corresponding proportions in the normative population, a comparison group of healthy children, using a one-sided binomial exact test.

Both univariate and multivariate analyses were conducted to study the unadjusted and adjusted associations, respectively, of the patient characteristics with the two outcomes. For univariate analysis, a logistic regression model was tested with the dichotomized BASC-2 PRS scores for anxiety and depression (i.e. elevated scores, defined as subscale scores ≥ 60 vs. not-elevated scores, defined as subscale scores <60) as dependent

variables, taking into consideration the dependence of repeated measurements at three timepoints for each participant. The following independent variables were considered in the model: age at diagnosis, gender, race/ethnicity, annual family income, maternal education, marital status of parents, therapeutic randomization, pain and hurt by parental report, nausea by parental report, as well as repeated measures of general family functioning and parental coping behaviors.

Similar logistic regression model was used for conducting the multivariate analysis. For the multivariate analysis, the patient and family factors that were associated with elevated anxiety and depression scores by univariate analysis at $p<0.1$ were tested as the independent variables in the multivariate regression modeling. All of the analyses were performed using SAS software, version 9.2.

Contributions to Methods

Patients were enrolled in the study by clinical research associates at each of the 31 participating sites in the United States and Australia. Research assistants at the sites also administered the surveys to families at each timepoint. The data was then sent to Yale. I created the databases and with the assistance of a more junior medical student, entered all the data. Beginning in 2011, I was also in charge of handling communication with the sites, which included tracking down missing data, reminding research assistants when timepoints were due, and sending necessary study materials to the sites. I developed the statistical plan with my mentor, but worked with a Children's Oncology Group (COG) statistician at the Statistical Center in Gainesville, Florida to do the data analysis.

I prepared an abstract with this data that was accepted for poster presentation at the American Society of Pediatric Hematology/Oncology annual meeting in New Orleans, LA in May 2012. In addition, I wrote the manuscript of this study with critical feedback from my mentor, Dr. Nina Kadan-Lottick, as well as our co-authors from the Children's Oncology Group. This manuscript is currently submitted to the Journal of Clinical Oncology.

RESULTS

Participants

The participants were a mean age of 4.9±2.2 years at diagnosis; 47.8% were female, 16.4% were of Hispanic ethnicity, 66.0% had married parents, and 45.3% had annual family incomes of less than $50,000 (Table 2).

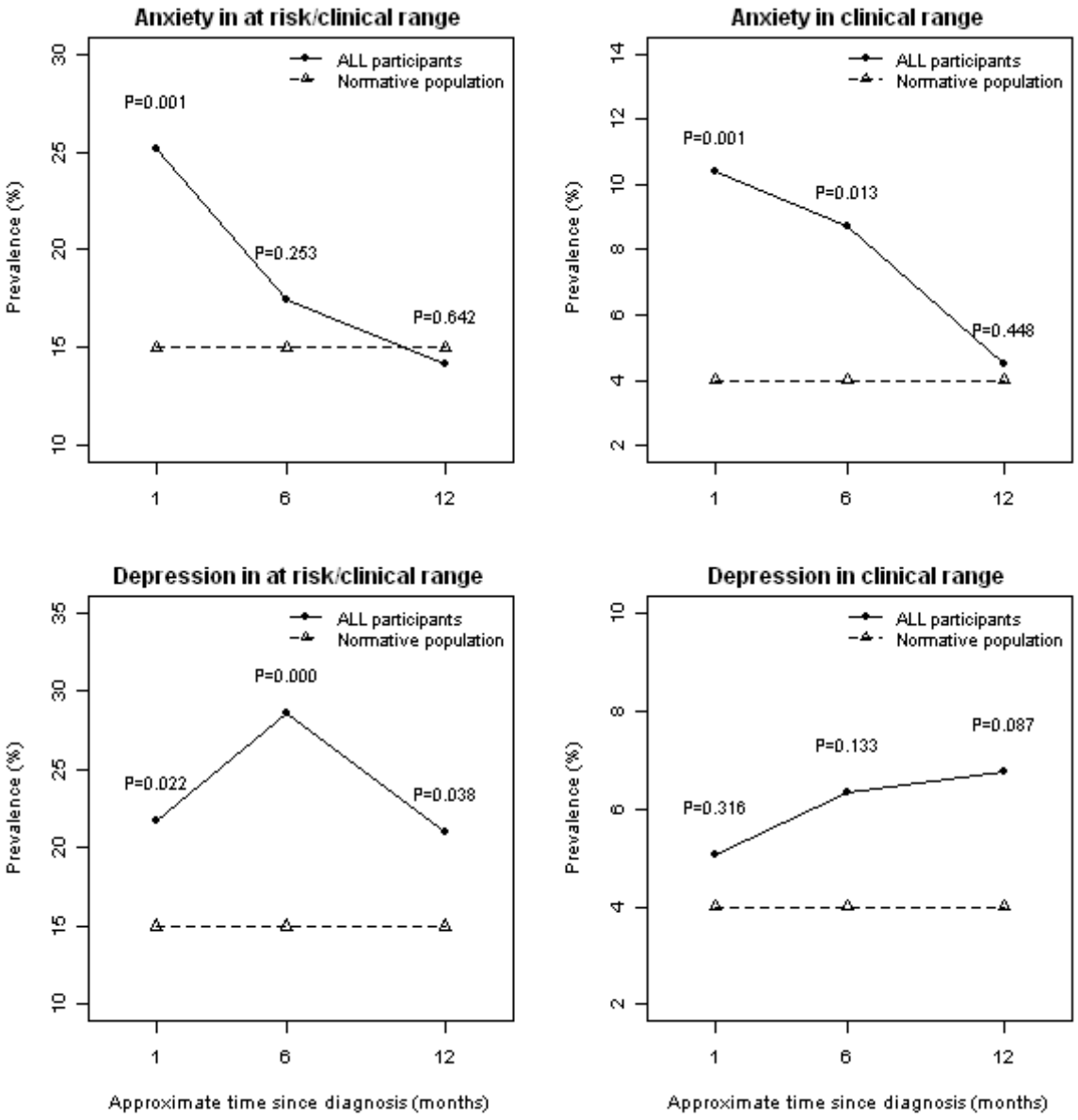
Frequency of Emotional Problems

Mean scores for anxiety and depression were stable and in the average range at all three timepoints. Mean anxiety scores were 53.2±12.7, 52.3±12.7, and 50.0±11.8 and depression scores were 52.1±11.1, 53.1±10.2, and 52.9±10.9 at one, six, and twelve months after diagnosis, respectively.

However, the frequency of elevated anxiety and depression scores was greater than expected in a normative population of children (Figure 2). Beginning at one month after diagnosis, a greater percentage of children scored in the *at-risk* or *clinically significant* range for anxiety (25.2% vs. 15%, p=0.001) than the normative population, but then reverted to expected levels at six (17.5% vs. 15%, p=0.253) and twelve months (14.2% vs. 15%, p=0.542) after diagnosis. The frequency of anxiety scores that were elevated to the *clinically significant* range was greater than expected at one month (10.4% vs. 4%, p=0.001) and six months (8.7% vs. 4%, p=0.013) after diagnosis, but then declined to expected levels by twelve months after diagnosis (4.5% vs. 4%, p=0.448).

For depression, a higher percentage of children had scores in the *at-risk* or *clinically significant* range than expected throughout the first year of therapy: one month (21.7% vs. 15%, $p=0.022$), six months (28.6% vs. 15%, $p<0.001$), and twelve months (21.1 % vs. 15%, $p=0.038$). However, the frequency of depression scores in the *clinically significant* range was not significantly different from expected levels at any timepoint: one month (5% vs. 4%, $p=0.316$), six months (6.4% vs. 4%, $p=0.133$), and twelve months (6.8% vs. 4%, $p=0.087$).

Figure 2. Rates of elevated anxiety and depression scores in the first year after diagnosis of ALL



Frequency of Behavioral Problems

Mean scores for hyperactivity and aggression were also stable and in the average range at all three timepoints. Mean hyperactivity scores were 47.4±7.3, 49.2±8.2, and 50.0±8.5 and aggression scores were 47.8±9.1, 48.9±9.2, and 49.6±9.1 at one, six, and twelve months after diagnosis, respectively.

Unlike anxiety and depression, the frequency of elevated hyperactivity and aggression scores was similar to that expected in a normative population. For hyperactivity, the percentage of children with scores in the *at-risk* or *clinically significant* range was 5.8 (95% CI, 1.9-9.7), 11.8 (95% CI, 6.2-17.4), and 8.2 (95% CI, 3.6-12.9) at one, six, and twelve months after diagnosis, respectively. This is compared to 15% expected in a normative population. Zero, 1.6 (95% CI, 0-3.7) and 3.7 (95% CI, 0.5-6.9) percent had hyperactivity scores in the *clinically significant* range at the three timepoints, versus 4% in the normative population. Similarly, for aggression, the percentage of children with scores in the *at-risk* or *clinically significant* range was 5.9 (95% CI, 1.9-9.8), 6.6 (95% CI, 2.7-11.0), and 9.2 (95% CI, 4.3-14.2) at one, six, and twelve months after diagnosis, respectively. This is compared to 13% expected in a normative population. 2.9 (95% CI, 0.1-5.6), 3.9 (95% CI, 0.5-7.3), and 3.0 (95% CI, 0.1-5.9) percent had aggression scores in the *clinically significant* range at the three timepoints, versus 4% in the normative population.

Since hyperactivity and aggression were not found to be significant problems, they were not included in the longitudinal, univariate or multivariate analyses.

Longitudinal Analysis

Compared to children with non-elevated anxiety scores, those with anxiety scores in the *at-risk/clinically significant* range at one month after diagnosis were 7.70 (95% CI, 2.39-24.85; $p<0.001$) times as likely to have elevated scores at six months and 7.11 times

(95% CI, 2.08-24.30; p=0.002) as likely to have elevated scores at twelve months after diagnosis. Children with elevated scores six months after diagnosis were 20.64 (95% CI, 6.02-70.74; p<0.001) times as likely to have elevated scores twelve months after diagnosis.

Compared to children with non-elevated depression scores, those with depression scores in the *at-risk/clinically significant* range at one month after diagnosis were 3.51 (95% CI, 1.33-9.26; p=0.015) times as likely to have elevated scores at six months and 3.31 (95% CI, 1.20-9.10; p=0.023) times as likely to have elevated scores at twelve months after diagnosis. Children with elevated scores six months after diagnosis were 5.11 (95% CI, 1.94-13.48; p<0.001) times as likely to have elevated scores twelve months after diagnosis (data not displayed)

Predictors of Anxiety and Depression by Univariate Analysis

Table 3 displays the results of the univariate analysis adjusted for time elapsed since diagnosis. The outcomes, anxiety and depression, were used as dichotomous variables (elevated vs. non-elevated scores). The independent variables were also transformed into dichotomous or categorical variables with several exceptions. The CHIP subscales, the "pain and hurt" scale, and the "nausea" scale are only valid as continuous variables. Therefore, they were inputted into the model as continuous variables. In this univariate analysis, significant predictors of anxiety and depressive symptoms included unhealthy family functioning and less reliance of each of the three coping patterns measured by the CHIP subscales. Hispanic ethnicity was significantly associated with worse anxiety

symptoms, but not depressive symptoms. Conversely, worse physical functioning as measured by the pain and hurt subscale of the PedsQL was significantly associated with depression, but not anxiety. There were no differences detected among the four treatment groups.

Table 3. Univariate association of patient and family factors with anxiety and depression

	Anxiety		Depression	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Age group at diagnosis				
Pre-school *(ages 2-4)*	Reference group		Reference group	
School-age *(ages 5-12)*	0.62 (0.37,1.05)	0.076	0.78 (0.49,1.26)	0.314
Gender				
Male	Reference group		Reference group	
Female	1.62 (0.97,2.72)	0.067	1.27 (0.79,2.02)	0.325
Race/Ethnicity				
White, non-Hispanic	Reference group		Reference group	
Hispanic	3.32 (1.80,6.15)	0.000	1.36 (0.73,2.53)	0.335
Black, non-Hispanic	0.83 (0.23,2.96)	0.769	1.22 (0.46,3.25)	0.696
Other	1.61 (0.68,3.83)	0.277	1.59 (0.75,3.37)	0.226
Annual family income				
≥$50,000	Reference group		Reference group	
<$50,000	1.11 (0.63,1.98)	0.720	1.17 (0.68,2.01)	0.564
Maternal education				
At least some college	Reference group		Reference group	
Less than college	1.15 (0.64,2.04)	0.642	1.24 (0.74,2.09)	0.410
Marital status of parents				
Married	Reference group		Reference group	
Not married	1.30 (0.74,2.29)	0.354	1.65 (0.99,2.75)	0.054
General Family Functioning[1]				
Healthy family functioning	Reference group		Reference group	
Unhealthy family functioning	3.01 (1.76,5.15)	<0.001	2.37 (1.45,3.85)	0.001
Maintaining family integration coping behaviors[2]	0.97 (0.94,0.99)	0.009	0.96 (0.94,0.98)	0.001
Maintaining social support coping behaviors[3]	0.96 (0.94,0.99)	0.005	0.95 (0.93,0.97)	<0.001
Understanding the medical situation coping behaviors[4]	0.95 (0.90,1.00)	0.038	0.93 (0.89,0.98)	0.003
Pain and hurt by parental report[5]	0.99 (0.98,1.00)	0.062	0.99 (0.98,1.00)	0.016
Nausea by parental report[6]	0.99 (0.97,1.01)	0.186	0.99 (0.98,1.01)	0.230
Therapeutic randomization[7]				
SC/SIM-SDI	Reference group		Reference group	
IC/SIM-SDI	1.20 (0.60,2.40)	0.598	0.95 (0.50,1.78)	0.862
SC/AIM-ADI	1.23 (0.59,2.57)	0.585	1.00 (0.51,1.95)	0.991
IC/AIM-ADI	1.02 (0.45,2.28)	0.970	1.14 (0.56,2.33)	0.713

[1]Measured by the FAD-GF. [2]Measured by the CHIP subscale 1. [3]Measured by the CHIP subscale 2. [4]Measured by the CHIP subscale [5]Measured by the PedsQL pain and hurt scale [6]Measured by the PedsQL nausea scale [7]SC = Standard Consolidation, IC = Intensified Consolidation, SIM-SDI = Standard Interim Maintenance and Standard Delayed Intensification, AIM-ADI = Augmented Interim Maintenance and Augmented Delayed Intensification

Predictors of Anxiety and Depression by Multivariate Analysis

Table 4 displays the results of a multivariate model, which included the patient and family factors that were at least marginally significant ($p \leq 0.1$) by univariate analysis: age, gender, marital status, race/ethnicity, the pain and hurt subscale, general family functioning, and the three CHIP subscales. In this adjusted analysis, Hispanic ethnicity (OR=3.35; 95% CI, 1.36-8.24) and unhealthy family functioning (OR=2.24; 95% CI, 1.07-4.70) remained significant predictors of worse anxiety symptoms.

The significant predictors of worse depressive symptoms by adjusted analysis were unhealthy family functioning (OR= 2.40; 95% CI, 1.26-4.56), unmarried parents (OR=2.36; 95% CI, 1.17-4.75), worse physical functioning (p=0.049), and less reliance on maintaining social support coping behaviors (p=0.004).

Table 4. Multivariate analysis of the association of patient and family factors with anxiety and depression

	Anxiety		Depression	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Age group at diagnosis				
Pre-school *(ages 2-4)*	Reference group		Reference group	
School-age *(ages 5-12)*	0.49 (0.24,1.01)	0.053	0.77 (0.42,1.40)	0.387
Gender				
Male	Reference group		Reference group	
Female	1.57 (0.79,3.16)	0.206	1.24 (0.68,2.25)	0.478
Race/Ethnicity				
White, non-Hispanic	Reference group		Reference group	
Hispanic	3.35 (1.36,8.24)	0.009	0.52 (0.20,1.39)	0.192
Black, non-Hispanic	0.85 (0.16,4.54)	0.846	0.86 (0.25,2.99)	0.815
Other	1.39 (0.42,4.52)	0.592	1.10 (0.42,2.87)	0.849
Marital status of parents				
Married	Reference group		Reference group	
Not married	1.15 (0.49,2.56)	0.797	2.36 (1.17,4.75)	0.017
General Family Functioning[1]				
Healthy family functioning	Reference group		Reference group	
Unhealthy family functioning	2.24 (1.07,4.70)	0.033	2.40 (1.26,4.56)	0.008
Maintaining family integration coping behaviors[2]	0.99 (0.94,1.05)	0.771	1.04 (0.99,1.10)	0.085
Maintaining social support coping behaviors[3]	0.98 (0.94,1.03)	0.366	0.94 (0.91,0.98)	0.004
Understanding the medical situation coping behaviors[4]	1.00 (0.90,1.10)	0.964	0.95 (0.88,1.04)	0.283
Pain and hurt by parental report[5]	0.99 (0.98,1.00)	0.152	0.99 (0.98,1)	0.049

[1]Measured by the FAD-GF. [2]Measured by the CHIP subscale 1. [3]Measured by the CHIP subscale 2.
[4]Measured by the CHIP subscale [5]Measured by the PedsQL pain and hurt scale

DISCUSSION

Summary of Findings

This is the first prospective, longitudinal study of emotional and behavioral functioning in a large sample of children with acute lymphoblastic leukemia to our knowledge. We found that depressive symptoms were a significant problem when first measured at the end of the first month of therapy, and remained at greater than expected levels at 6 and 12 months after starting treatment. We found that anxiety was a significant problem at the end of the first month of therapy, but then its prevalence declined to levels expected in a normative population at 6 and 12 months after starting treatment. In addition, we found that children with elevated anxiety and depression symptoms at one month after diagnosis were significantly more likely to continue to have elevated symptoms throughout the first year of therapy. In adjusted analysis, we found that the strongest predictors of emotional functioning were family functioning and self-reported Hispanic ethnicity. Children whose parents reported unhealthy family functioning were 2.24 times at likely to have anxiety symptoms and 2.40 times as likely to have depressive symptoms. Hispanic children were 3.35 times as likely as white, non-Hispanic children to have anxiety symptoms, but were not at increased risk for depressive symptoms. We did not find that age, gender, or family socioeconomic status predicted emotional functioning. In addition, we did not find behavioral changes to be a significant problem.

Strengths of Current Study

Our study is unique in that all participants had the same diagnosis with a high-expected cure rate, and were enrolled on a randomized clinical trial. Thus, unlike previous studies

that used heterogeneous populations, we were able to account for any differences due to therapeutic randomization. In addition, since we enrolled patients at 31 sites that represented a range of community and tertiary-care centers and rural and urban regions, our study can be generalized more than single institution studies. Furthermore, we had a high participation rate (82% of eligible), which greatly reduced but did not eliminate the potential for selection bias.

Comparison of Results to Existing Longitudinal Data

Limited published data are available regarding the longitudinal psychosocial functioning of children currently receiving chemotherapy. Our results can be most closely compared with the prospective, cohort study of 38 patients by Sawyer et al in South Australia (23, 25). Consistent with our study, Sawyer et al found that children experience considerable emotional distress in the immediate post-diagnosis period. However, unlike our finding that depression was present at levels higher than expected throughout the first year, Sawyer et al found that by one year after diagnosis, children treated for cancer had similar psychological functioning as children in the community. The Sawyer et al study had limitations that our study overcame including: a small, heterogeneous sample and utilization of an instrument that was confounded by physical symptoms and did not distinguish between anxiety and depression symptoms.

Evaluation of Family Functioning Findings

To the best of our knowledge, this is the first study that reported family functioning as a predictor of emotional functioning of children with cancer. Previous research on family

functioning has focused on it as an outcome variable. There is one study that examined the role of family functioning on quality of life in children who recently completed chemotherapy, but it found both positive and negative correlations depending on the age group of the child (32). In other populations such as pediatric asthma patients, family dysfunction has been associated with children's mental health (50). Our study used the General Functioning Scale of the Family Assessment Device, which measures perceived family cohesion and ability of family members to communicate with each other. Our results suggest that families who demonstrate worse cohesion and communication should be considered higher-risk and be offered more psychosocial support. There are psychosocial risk screening measures that have been developed, such as the validated and widely published Psychosocial Assessment Tool (PAT2.0), which can integrate assessments of family functioning (51). Furthermore, as previously discussed, family functioning may be a modifiable variable, and thus, our results support using or developing family-based interventions that target family functioning.

Although anxiety and depressive symptoms may lessen throughout therapy, it is important to recognize the distress they cause and provide appropriate psychosocial interventions. The NIH consensus statement on cancer symptoms states: "All patients with cancer should have optimal symptom [includes pain, depression, and fatigue] control from diagnosis throughout the course of illness, irrespective of personal and cultural characteristics" (52). A wealth of psychosocial interventions exists for children with cancer, which include using cognitive-behavioral therapy, social-recreational activities, and psychoeducational interventions (53). Many interventions use family-based

methods, which have been associated with beneficial outcomes for children (54). Understanding the efficacy of various interventions is an ongoing area of research (53).

Evaluation of Ethnicity Findings

The significant association of Hispanic ethnicity with anxiety is novel in children with ALL. There is a single report that showed poorer emotional functioning in Hispanic children with cancer, but it only addressed the off-treatment period (55). We do know, however, that there are other differences between Hispanic and non-Hispanic children with ALL, including inferior survival rates in Hispanic children (1, 56). We do not have the data available to explain how Hispanic ethnicity leads to worse psychological functioning, but given these differences, this area of study deserves further attention.

Limitations

The current study has some methodological characteristics that should be considered in interpreting the results. First, some patients enrolled in the study did not complete the evaluations at all the required timepoints. This was due to a combination of withdrawals from the therapeutic study, administrative errors at study sites, and incomplete forms. We also used parent-report measures instead of child self-report because the majority of children in our study were too young to complete a validated self-report evaluation. In addition, we were able to associate family functioning with emotional functioning, but we were not able to determine the direction of the association from our data. It may be that children with better emotional functioning lessen the burden on their families.

Conclusions and Implications

From this large, multisite, cohort study of children treated for SR-ALL, we conclude that symptoms of depression and anxiety are a significant problem in the immediate post-diagnosis period. While anxiety symptoms lessen after the first month of therapy, depressive symptoms persist throughout at least the first year. We also found that we can identify children at one month after diagnosis who are substantially more likely to have worse psychological functioning as manifested by anxiety and depression throughout the first year of therapy. These findings provide for a compelling rationale to screen children with SR-ALL for psychological problems soon after diagnosis and to develop early interventions to target anxiety and depressive symptoms. Furthermore, our results highlight high-risk groups who should receive additional psychosocial support. We also found that unhealthy family functioning is significantly associated with anxiety and depression. Therefore, more studies elucidating evidence-based family interventions for this population are needed, as are similar studies in other subtypes of pediatric cancer.

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