

ORIGINAL ARTICLE

Quality of life in children with acute lymphoblastic leukemia during induction therapy with PedsQL Cancer Module[®]

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Abstract

Background. Survival of children with acute lymphoblastic leukemia (ALL) is 80% in accordance with actual protocols. We ignore quality of life (QoL) during these chronic treatments, especially in our institution. The aim of this pilot study was to measure QoL in stable children with ALL during the first part of treatment (induction therapy) with PedsQL Cancer Module[®].

Methods. We took two measurements in children with a recent diagnosis of ALL and determined changes in the QoL between the beginning and the end of induction therapy. We included 26 patients from 2 to 18 years of age with ALL (2 weeks and 2 months after diagnosis) and divided them into four groups: 2-4 years, 5-7 years, 8-12 years, and 13-18 years of age.

Results. In the second measurement, we observed a better QoL in relation to an adaptation process in the child and remission of symptoms.

Conclusions. PedsQL Cancer Module[®] was a useful instrument for measuring QoL and detected changes in children with ALL during induction therapy.

Key words: leukemia, lymphocytic, acute leukemia, lymphoblastic, acute induction therapy quality of life; PedsQL Cancer Module[®].

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant neoplasm characterized by a cytogenetic alteration that causes an abnormal monoclonal proliferation of precursor lymphoid cells and infiltrates >25% of the bone marrow. It is the most common malignant neoplasia in children and represents 25% of all cancers in children.¹ In Mexico, ALL ranks seventh in mortality of children aged 1 to 4 years old with a rate of 3.2/100,000 inhabitants. In children 5-14 years of age, it is the second leading cause of death, only after motor vehicle accidents, with a rate of 2.7/100,000

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inhabitants.² At the Hospital Infantil Mexico Federico Gomez (HIMFG), epidemiology is similar to that described in the literature and this hospital receives >80 patients per year who are diagnosed with ALL.

The treatment of leukemia is divided into four periods: remission induction, intensification, consolidation and maintenance; and its overall length is ~3 years.³ In this study we conducted research on children who were at the stage of remission induction. Chemotherapy administration during remission induction in HIMFG takes place in the ambulatory chemotherapy service, an area of the hospital specifically designated for this purpose.

Survival in children with cancer has significantly improved in recent years. This has been attributed to the organization of specialized centers with multidisciplinary teams and development of programs based on numerous clinical trials^{4,5} especially in children with ALL. We have had a breakthrough due to improved understanding of its physiopathology, development of new chemotherapy agents and improved supportive care for patients.¹ Currently, the survival rate for patients with ALL is >80%.⁶

During treatment, most children experience adverse side effects, not only physical but also emotional, especially because it is a chronic treatment. The most important side effects are pain, lack of energy to enjoy activities of daily living and fears for what the future holds. In addition to the effects on the child, parents also experience feelings such as depression and anxiety, especially during the first months after disease diagnosis and especially when accompanying their child to the hospital, missing work and trying to understand the medical management of their child at home.⁵

In 1948, the WHO defined health as complete physical, mental and social wellbeing and not merely the absence of disease. This concept has evolved to quality of life (QoL), which includes a functional health status, perception of good health, life satisfaction and ability to compete. Both the general perception of health as well as vitality, pain and disability can be influenced by personal experiences and the expectations of a person. That is why the concept of QoL requires a method of reliable and valid assessment that involves the person being evaluated.⁷

Because many of the components of QoL cannot be observed directly, they are evaluated through questionnaires that contain a series of questions and eventually assigned a final score that is interpreted according to previously established values.

Recently, there have been studies of QoL in pediatric patients with cancer, but most have focused on survivors and terminally ill patients.⁸ There have been few studies conducted during the treatment phase of the illness. In these recent studies, we have seen that the QoL is less in patients with active treatment than in those survivors who have completed treatment.⁶ Unlike adults, measurement of QoL in pediatric patients should be done via a multidimensional model and at the same time adapted to the age group, using a model such as PedsQL Cancer Module[®].

The PedsQL[®] and the PedsQL Cancer Module[®] have been used to assess QoL in children with different nosological diseases. In a multicenter study, Varni⁹⁻¹¹ evaluated the reliability and validity of the PedsQL Cancer Module[®] by applying it to 339 children 2-18 years of age with cancer (50% with ALL) who were in treatment and in remission, compared with a group of healthy children. The questionnaire was able to identify healthy children from sick children, and those who were in treatment from those without treatment.

Another study published in April 2008 compared three measurement stages of QoL (Pediatric Quality of Life Inventory-PedsQL, Child's Health Questionnaire-CHQ, and Health Utilities Index- HUI) in children with cancer (62% with ALL) during chemotherapy.¹² Measurements were made weekly during the first 4 weeks after the third day of diagnosis and found that the PedsQL[®] was the one that had greater sensitivity in detecting changes in QoL in patients.

In 1996, in the Centro Medico Nacional Siglo XXI (CMNXXI) of the Instituto Mexicano del Seguro Social (IMSS), the Dartmouth-COOP questionnaire was validated, evaluating the functional biopsychosocial status in school-age children and adolescents with chronic disease (leukemia, lymphoma, solid tumors, neuropathies, etc.), finding that QoL can be measured in similar ways as in adults.¹³

In 1999, in the HIMFG, a study was conducted to assess the QoL of patients with chronic diseases such

as asthma, T1DM, leukemia and HIV/AIDS through various generic and specific questionnaires. Patients with leukemia showed differences depending on their stage of treatment; patients presented lower scores when they were in remission induction than those patients who were undergoing maintenance.¹⁴ Similarly, in 2001 the QoL of adolescents with chronic diseases was evaluated. It was a review of the concept of QoL in adolescents with some degree of disability due to chronic illness and of the methods they developed to evaluate them.⁷ In 2002, a cross-sectional study of 23 children with terminal phase leukemia of two IMSS hospitals was published. The objective of the study was to assess the QoL of those who were treated at the hospital in relation to those who were managed at home, with the latter resulting in the highest scoring in QoL questionnaires.¹⁵

Optimal treatment of children with ALL requires attention in several areas of supportive care, including transfusions, infectious complications, metabolic and nutritional requirements, and ongoing psychosocial support and understanding from the patient and family.¹

Supportive care refers to treatment designed to prevent and control adverse effects from the cancer and its treatment. These effects not only cause discomfort to the patient but may also interfere with the proper administration and planning of the chemotherapy. In order to achieve optimal therapeutic goals and improve QoL, it is imperative that these adverse effects are managed appropriately.^{16,17}

Currently, we tend to evaluate a person beyond their physical ability and take into account their social context, self-esteem, mental health and social supports.

Although the terms “health status,” “functional status” and “QoL related-health” have been used interchangeably, a distinction between these terms is needed because the first two refer only to the physical condition of the patient, whereas the last term is associated with QoL and refers to the perception of the patient’s impact of their illness and treatment on various aspects of life: physical, emotional, social, functional role, etc.⁶

The PedsQL[®], in the version for cancer patients (PedsQL Cancer Module[®]), is a multidimensional model that

contains stages that evaluate physical, emotional, social and school functioning of the patient. There are many advantages to this model such as its brevity (few reagents in comparison to other models), practicality (4 min to answer it), flexibility (designed for use in the community, school, and clinical practice), appropriate for each age group (modules for 2-4, 5-7, 8-12 and 13-18 years), multidimensionality (assessing the physical, emotional, social and school status), reliability (internal consistency of 0.88 in the reporting of children and 0.90 for the parents) and validity (distinguishes between healthy children and those with acute and chronic diseases). Moreover, it distinguishes the severity level of chronic diseases.¹⁶

Questionnaires include different versions for each age group who were asked about symptoms that occurred during the previous month and during the previous 7 days. The scores were given according to a 5-point scale: from 0 (never been a problem) to 4 (almost always has been a problem). In order to obtain a score, these were transformed into linear scales (LS), inverse of 0-100, with 100 being the highest rating and representing the best QoL. Each value was assigned a score in the following form: 0 = 100, 1 = 75, 2 = 50, 3 = 25 and 4 = 0. Total score is the result of the total of the LS.

The PedsQL 3.0 Cancer Module[®] is the latest model applicable to cancer patients, including more variables to assess QoL in these types of patients. This model is also multidimensional and evaluates eight stages: pain and discomfort, presence of nausea, anxiety about procedures, anxiety about treatment, worry, cognitive problems, perception of physical appearance and communication.¹⁶

Objectives

We undertook this study to measure QoL in patients with newly diagnosed ALL who come to the Servicio de Quimioterapia Ambulatoria (Outpatient Chemotherapy Service) at the HIMFG using the PedsQL Cancer Module 3.0[®] and to determine whether it changes from week 2 and the 2nd month after diagnosis.

Patients and Methods

We carried out an observational, descriptive, prolective and prospective pilot study. Patients were consecutively enrolled as opposed to randomized. We included children (2-18 year of age) who were diagnosed with ALL for the first time and whose diagnosis was made in

the HIMFG from September 2007 to January 2008. We excluded children with neurological ailments or cognitive aggregates or other chronic diseases, which were found in terminal stages or in patients unable to receive treatment. Also excluded were those who had criteria that required hospitalization or were unstable during the time of the interview. Patients were eliminated who, for some reason (death, study withdrawal, change of address, etc.), were unable to answer the second questionnaire.

We applied the PedsQL Cancer Module 3.0[®] to all patients in the study. They were divided into four age groups according to the questionnaires: 2-4 years, 5-7 years, 8-12 years and 13-18 years old. The first evaluation was performed 2 weeks after initial diagnosis and the second one 2 months later. The investigator administered the questionnaire in a standardized manner under the same conditions. Informed consent was also obtained. The questionnaire was answered in ~4 min. For those who could not read or write, the questions were read out loud to them and the answers were recorded in the questionnaire by the interviewer. We excluded questionnaires that were

incomplete.

After completing the questionnaire, as the scores are found in 5-point scale from 0 (never been a problem) to 4 (almost always been a problem), they were transformed into inverse linear scales of 0-100, with 100 being the highest rating and representing the best QoL. Each value was assigned a score as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0. The total score is the result of the sum of the linear scale. Scores were obtained for the two measurements in this manner.

We conducted a pilot study with 26 patients to determine the applicability of the questionnaire PedsQL Cancer Module 3.0[®] so that, in the future, a study can be designed based on these results with a calculation of adequate sample size.

We made the description of the variables using measures of central tendency and dispersion, with calculation of averages and standard deviation for normally distributed variables and by using measurements of minimum and maximum values for categorical variables. According to the results we performed the Wilcoxon test.

Table 1. PedsQL Cancer Module 3.0[®] evaluation of children with ALL at 2 weeks and 2 months after diagnosis

	Minimum	Maximum	Average	SD
First measurement (2 weeks)				
Pain	0	200	137.50	74.91
Nausea	250	500	466.35	65.93
Procedure anxiety	0	300	74.04	103.31
Treatment anxiety	0	300	193.27	115.01
Preoccupation	0	300	253.85	83.87
Cognitive problems	0	500	326.92	131.51
Physical appearance	125	300	267.31	61.95
Communication	0	300	210.58	90.87
Total	1 100	2 625	1 929.81	323.88
Second measurement (2 months)				
Pain	0	200	168.27	60.64
Nausea	300	500	478.85	45.65
Procedure anxiety	0	300	146.15	105.04
Treatment anxiety	75	300	262.50	68.64
Preoccupation	0	300	269.23	80.09
Cognitive problems	200	500	356.73	96.83
Physical appearance	50	300	257.69	73.74
Communication	150	300	281.73	40.96
Total	1825	2700	2221.15	251.36

A modification of the QoL was interpreted as a significant difference ($p < 0.05$) between the first and second measurement of the results of the questionnaire.

Results

Fifty two questionnaires were analyzed from 26 patients. Of the 26 cases evaluated, 14 were from female patients and 12 from males. The male:female ratio was 1:1.16 and the median age was 6 years (range: 2-14 years).

Age distribution was as follows: group 1 (2-4 years old) consisted of eight patients, group 2 (5-7 years old) had nine patients, group 3 (8-12 years old) had six patients, and group 4 (13-18 years old) had three patients; 53.8% had AA L1 and 46.2% had ALL L2.

With regard to the domains of PedsQL Cancer Module 3.0[®], these are shown in Table 1 and are abbreviated with the number 1 for the domains that are the result of the first measurement (after two weeks of diagnosis) and with the number 2 for results that were obtained from the second measurement (at 2 months after diagnosis). Items marked in the questionnaires became inverse linear scales as previously mentioned. The table also describes the average minimum and maximum for each item.

Table 2 shows the overall averages of the four groups of patients, comparing the first measurement with the second. The total value of the sum of the first

measurement was 1929.81 ± 323.88 (minimum 1100 and maximum 2625), whereas for the second measurement the average was 2221.15 ± 251.36 (minimum 1825 and maximum 2700).

Discussion

The population studied has the characteristics described in the literature except for some differences regarding the type of selection that is not random and the small number of individuals included. One notable difference is the slight predominance of females to males and the slight predominance of patients between 5 and 7 years old vs. children between 2 and 5 years. Another difference is the proportion of patients with ALL L1 and ALL L2 because the literature describes 85% of the cases as L1.

It is noteworthy that the scores we found in the two measurements are almost three to four times higher than those reported by Varni⁹ in children at the Cancer Center in Los Angeles. It is also worth noting that, in that study, they included patients with various neoplasms and in different stages of treatment. There have been reports of low scores in patients with leukemia and central nervous system (CNS) tumors.¹⁷ Lower scores are reported in the study from Brazil in 2007, which demonstrated the validity of the PedsQL Cancer Module[®] with relation to cancer patients who were receiving treatment and also those who had not been treated for over 12 weeks, and the correlation of the caregiver's score with the child's score. It also emerged that "nausea", "anxiety

Table 2. PedsQL Cancer Module 3.0[®] evaluation in children with ALL: comparison of the results between 2 weeks and 2 months of diagnosis

	First measurement (2 weeks)	Second measurement (2 months)	p value
Pain	137.50 ± 74.91	168.27 ± 60.64	0.193
Nausea	466.35 ± 65.93	478.85 ± 45.65	0.177
Procedure anxiety	74.04 ± 103.31	146.15 ± 105.04	0.001
Treatment anxiety	193.27 ± 115.01	262.50 ± 68.64	0.022
Preoccupation	253.85 ± 83.87	269.23 ± 80.09	0.109
Cognitive problems	326.92 ± 131.51	356.73 ± 96.83	0.046
Physical appearance	267.31 ± 61.95	257.69 ± 73.74	0.242
Communication	210.58 ± 90.87	281.73 ± 40.96	0.002
Total	1929.81 ± 323.8	2221.15 ± 251.36	0.001

Data are presented as average ± SD.

Wilcoxon test was used to compare two independent variables.

Measurement of quality of life showed higher scores in the second measurement in all areas. Nevertheless, only significant were those scores for procedure anxiety, treatment anxiety, cognitive problems and communication. Note that the overall score was significantly better for quality of life at 2 months after completion of the questionnaire.

about procedures” and “anxiety about treatment” were the most reliable items to discriminate between patients with/without treatment.¹⁸⁻²⁰

Overall, all the QoL scores improved between the first measurement and the second one. Anxiety about procedures, treatment anxiety, cognitive problems, communication and the addition of QoL resulted to be significant. With regard to nausea, there were no statistically significant results between the two measures; however, it was interesting to note that those were the ones that had high scores. This is very important because it is a preventable symptom.

Improvement in scores, in terms of anxiety, is probably due to a child’s adjustment to his/her environment. In addition, repetitive procedures (taking medications, medical examination, bone marrow aspirates, intrathecal chemotherapy administration, etc.) make children abandon their fear of the unknown. Communication problems improve as the child observes that he/she is in a situation where there is no intention to hurt him/her or is treated inappropriately. On the contrary, the child’s welfare is being taken care of. Improvement in cognitive problems score may be due to the fact that when patients are first diagnosed they think only of their illness and the situation they are in and forget about other activities (playing, school, reading, etc.). These four domains are very interesting because they are situations that can be improved by physician/patient relationships.

On the other hand, pain and nausea, which are common symptoms present in this stage of the disease and treatment, appear to have no major changes due in part to the proper administration of antiemetic drugs and analgesics or because pain is not a common manifestation for leukemia in these patients.

The reasons for concern also did not show any changes. This may possibly be explained because the majority of patients were <8 years of age and before reaching puberty children are not very reflective but have more concrete thoughts. Physical appearance also did not show a significant change. This is probably explained because the HIMFG is an oncology reference center where there are many patients with similar characteristics, and chemotherapy is administered in a special location that fosters a friendly environment for patients and families.

Finally, we must consider that in the evaluation of the QoL there may be great variability because this is a subjective experience and, at the same time, especially in children with ALL, they may be affected by both the disease and by the treatment.

In conclusion, we may mention that QoL is a concept that includes biopsychosocial interactions and can be evaluated using appropriate measurement instruments. In children with chronic diseases such as cancer, it is very important because it requires ongoing assessments regarding improvement and deterioration of their functional status caused by both the disease and the treatments. The PedsQL Cancer Module[®] used in patients with ALL undergoing remission induction proved to be a useful tool to measure QoL and was able to detect differences in the QoL during overall treatment along some aspects of its comprehensive evaluation.

Ethical Considerations

Anonymity of patients was guarded at all times. No procedures were performed during the administration of the questionnaires that would have interfered with the development of the interview. If we had noticed any deterioration in the clinical or psychosocial status of a patient, we would have reported them to the multidisciplinary team who handled the patients. Similarly, if it had detected that the QoL of a patient worsened dramatically during the two measurements, we would have alerted the administrators of the Oncology Department.

Limitations of the Study

The study evaluated ambulatory patients, this being important because they may have a better perception of the QoL of patients with the same diagnosis who had been hospitalized. Also, there is some bias in that patients were recruited as they were admitted to the Ambulatory Chemotherapy Service and diagnosed within a given period; they were not a random sample. Only patients with ALL and in remission induction were evaluated, limiting the assessment to these children and excluding those who, for example, have AML and required another type of chemotherapy.

The sample of patients was small; therefore, it is necessary to recruit more patients to give greater explanatory power to the study.

This was a pilot study where the QoL was determined

only on two occasions: at 2 weeks and 2 months after the initial diagnosis with little time for analysis, taking into account that QoL measurements were performed transversally and were dependent on many factors. There could have been more patients included, and more measurements could have been obtained because QoL has a dynamic connotation.

This study was conducted in a group of patients

with ALL, which is a disease with serious clinical manifestations. Improvement in the QoL may be related to clinical improvement of patients who are beginning treatment.

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