Compliance with a protocol for acute lymphoblastic leukemia in childhood

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Background: *Remission rates achieved after the initial treatment of acute lymphoblastic leukemia may be similar in both developed and developing countries, but relapse rates are much higher in the latter. Thus, other reasons are needed, in addition to biological characteristics of the leukemic cells themselves, to explain the unfavorable evolution of patients living in unfavorable socioeconomic and cultural conditions.*

Objective: *The aim of this study was to retrospectively evaluate compliance to an acute lymphoblastic leukemia treatment protocol.*

Methods: *Main abstracted data were: total duration and reasons for interruption of chemotherapy, prescribed doses of 6-mercaptopurine, and median white blood cell and neutrophil counts during the maintenance phase. Interruptions of chemotherapy were considered inappropriate if they did not follow predetermined criteria established in the protocol.*

Results: *Fourteen of 73 patients (19.2%) unduly interrupted chemotherapy by determination of their physicians. The median white blood cell count was higher when compared with the protocol recommendations; the median 6-MP dose was lower than the standard recommended dose. The estimated probability of event-free survival was higher for patients with lower median leukocyte counts and close to those predetermined by the protocol. Event-free survival was also higher for children with a higher percentage of days without chemotherapy due to bone marrow or liver toxicity excluding undue interruptions. In multivariate analysis, both factors remained statistically significant. These results suggest that the intensity of maintenance chemotherapy may not have been enough in some children, to achieve adequate myelosuppression, hence the observation of higher leukocyte counts and none or rare episodes of therapy interruption.*

Conclusions: *Compliance to the therapeutic protocol by both doctors and patients should always be considered in the evaluation of therapeutic failure in acute lymphoblastic leukemia; strict adherence to treatment protocols contributes to better treatment results in acute lymphoblastic leukemia children.*

Keywords: *Guideline adherence; Chemotherapy; Precursor cell lymphoblastic leukemia-lymphoma; Antineoplastic combined chemotherapy protocols*

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. Currently, about 80% of newly diagnosed patients achieve a cure.[1,2]

Remission rates achieved after the initial treatment of ALL may be similar in both developed and developing countries, but relapse rates are much higher in the latter, even with the use of similar treatment protocols. Thus, other reasons are needed, in addition to biological characteristics of the leukemic cells themselves, to explain the unfavorable evolution of ALL patients living in unfavorable socioeconomic and cultural conditions. Factors such as poor access to health services and treatment, misuse of medications, and noncompliance of the patient, family and/or health professionals to protocols should be considered.[3,4] Noncompliance can increase the chances of relapse and results in incorrect assessments of chemotherapy effectiveness.[5,6]

The present study focuses mainly on medical adherence, since there are few studies in the literature evaluating the influence of this factor on the prognosis of ALL.[7,8] The overall aim of this study was to evaluate adherence among physicians and patients/families to the childhood ALL treatment protocol used at the Hospital das Clinicas, Universidade Federal de Minas Gerais (HC-UFMG), Brazil from 1997 to 2001.

Methods

This is a retrospective study with data obtained from analysis of medical records of the Hematology Service, HC-UFMG. The study was approved by the university's Research Ethics Committee.

Conflict-of-interest disclosure:
The authors declare no competing financial interest

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The study population comprised children and adolescents with ALL diagnosed at the HC-UFMG from October 1996 to December 2000. All patients were submitted to the treatment protocol prescribed by the Brazilian Cooperative Group for the Treatment of Childhood Leukemia GBTLI-93 and, without exception, had free access to medications. The prescription of chemotherapy was made by pediatric hematologists or hematology residents under the supervision of experienced hematologists. The study included only 73 patients who began the chemotherapy maintenance phase after induction and consolidation/ intensification as in the protocol; this was 83% (73/88) of patients diagnosed at our institution over the said period.

Patients in this study, with the exception of one, were the same as those reported on in a paper published by the authors establishing the frequency of thiopurine methyltransferase (TPMT) gene mutations in a population of 116 patients with ALL.[9]

The maintenance phase was based on the use of 6-mercaptopurine (6-MP) at an initial dose of 50 mg/m^2/day orally, and methotrexate (MTX) at a dose of 25 mg/m^2/week, intramuscularly. Doses should be adjusted in order to maintain the leukocyte count from 2-3 x 10^9/L and the phagocyte count above 0.5 x 10^9/L.

For each patient, the following variables were evaluated: 1) mean of the prescribed doses of 6-MP: the sum of all doses/ m^2 divided by the duration of the maintenance phase of chemotherapy in days; 2) mean doses of MTX: the sum of all doses/m^2 divided by the total cumulative dose for the duration of the maintenance phase in weeks; 3) duration of interruption of chemotherapy during the maintenance phase: percentage of days on which the patient did not receive 6-MP and MTX in relation to the total duration of the maintenance phase; 4) median leukocyte and neutrophil counts with tests being performed at least monthly during the maintenance phase; 5) reasons for interruption of chemotherapy during the maintenance phase. We considered undue interruptions as those that did not meet the following criteria established by the protocol: a) total leukocyte count < 1.5 x 10^9/L and total phagocytes < 0.5 x 10^9/L; b) oral mucous ulceration; c) suspicion of severe infection; d) liver dysfunction characterized by elevation of transaminases above 300 U/mL; e) platelet count < 50 x 10^9/L; 6) duration of interruption of maintenance therapy for reasons specified by the protocol (item 5), equivalent to the difference between the percentage defined in item 3 minus the percentage of undue interruptions, whether motivated by physicians or as admitted by the family and registered in the files.

The Kaplan-Meier method was used to estimate overall survival (OS) and event-free survival (EFS) from the start of maintenance chemotherapy. Events were defined as death or disease recurrence. The log rank test was used to compare survival curves. The Cox method was used to analyze the prognostic influence of a continuous single variable on EFS. In both cases, p-values < 0.05 were considered statistically significant. Variables whose level of statistical significance in univariate analysis was a p-value < 0.2 were included in the initial multivariate Cox model and kept in the final model if the p-value < 0.1.

Results

Of the 73 patients studied, 43 (58.9%) were female. The median age at diagnosis was 4 years (1.3 to 16.3 years). Immunophenotyping was performed in 63 cases and 47 of these patients (63%) had pre-B CD10$^+$ leukemia. The median time of follow-up until May 2007 was 7.5 years (1.3 to 11.3 years).There was no loss to follow up for this series.

Twenty of 73 patients had disease recurrence. Sixteen of these 20 children died. The deaths resulted from complications related to relapse. The estimated probability of overall survival at 8 years from the start of maintenance chemotherapy for the entire group was 77.1% ± 5.6%. The probability of EFS for the whole group was 72.6% ± 5.2%.

Twenty-seven of 73 patients (37%) had chemotherapy maintenance suspended at least once for reasons considered inappropriate. Of these, 14 patients (19.2%) interrupted chemotherapy at least once by determination of the physician. On considering the number of interruptions, we found that 41 cases did not fit the protocol criteria, with 20 being determined by medical staff and 21 by the patients' relatives without any medical advice.

It is worth mentioning that aminotransferase below levels pre-established by the protocol for adjusting the chemotherapy doses, and leukopenia and neutropenia, with values above the cutoff levels in the protocol were used as reasons for undue interruption of chemotherapy by physicians (Table 1).

The percentage of total days of interruption of the chemotherapy (including both the undue interruptions and those that met protocol criteria) ranged from 0 to 19%

Table 1 - Reasons for the 41 episodes of undue suspension of chemotherapy during the maintenance phase of treatment in 27 of 73 children with acute lymphoblastic leukemia

Reason for suspension of chemotherapy	Number of suspension episodes (%)
Chemotherapy suspended by family members without any medical advice (total)	21 (51.2%)
Chemotherapy suspended by physicians (total)	20 (48.8%)
Decreased leukocyte and/or neutrophil count, but with values still above the limits set by the protocol	6 (14.6%)
Elevated aminotransferases, but with values still below the limits set by the protocol	6 (14.6%)
Reason not specified on the patient's chart	4 (9.8%)
Upper respiratory infection	3 (7.3%)
Bronchitis	1 (2.4%)
Total	41 (100%)

(interquartile range 4.4% to 9.95%). Excluding the days of undue interruption from the calculation, leaving only the percentage of days of "appropriate" chemotherapy interruption, i.e., those that followed the protocol norms, the scores ranged from 0 to 18.7% (interquartile range 3.46% to 9.0%). The longer the "appropriate" suspension of chemotherapy, the lower the likelihood of relapse (Cox model; p-value = 0.04). For graphical display, this variable was dichotomized into two strata: children with less than or more than 2% of "appropriate" chemotherapy interruption. This interruption equals a two-week break for children who completed the whole of the maintenance phase. The probability of EFS for the group with less than 2% of interruption was 33.3 ± 13.6% (8 relapses in 12 children). For the group with more than 2% of interruption, the EFS was 80.3% ± 5.1% (12 relapses in 61 children; p-value = 0.0001 - Figure 1).

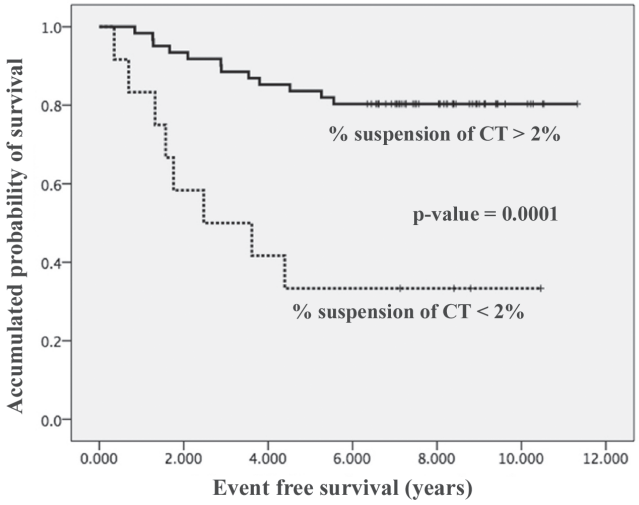

Figure 1 – Event-free survival (EFS) curves for children with acute lymphoblastic leukemia according to Kaplan-Meier method. The vertical lines on the curves represent patients alive in first remission. The probability of EFS for patients who had "appropriate" chemotherapy (CT) suspensions for a period of more than 2% of the total duration of the maintenance phase (n = 61) was 80.3% ± 5.1% and for the group with interruptions below this value it was 33.3% ± 13.6% (n = 12; p-value = 0.0001)

The median leukocyte count of each child in the maintenance phase of chemotherapy ranged from 2.3 to 7.0 x 10^9/L (median of entire group: 3.5 x 10^9/L). The probability of EFS for the subgroup with a median below 3.5 x 10^9/L was 83.3% ± 6.2%; for those with a median above 3.5 x 10^9/L, it was 62.2% ± 8.0% (p-value = 0.03 - Figure 2).

The mean prescribed dose of 6-MP for the entire group of patients during the maintenance phase of treatment ranged from 18.5 to 74.9 mg/m^2/day (median for the whole group was 47.8 mg/m^2/day). The probability of EFS was 80.5% ± 6.6% for the group of patients with an average below 47.8 mg/m^2/day; for those with an average of more than 47.8 mg/m^2/day, it was 64.8% ± 7.8% (p-value = 0.15).

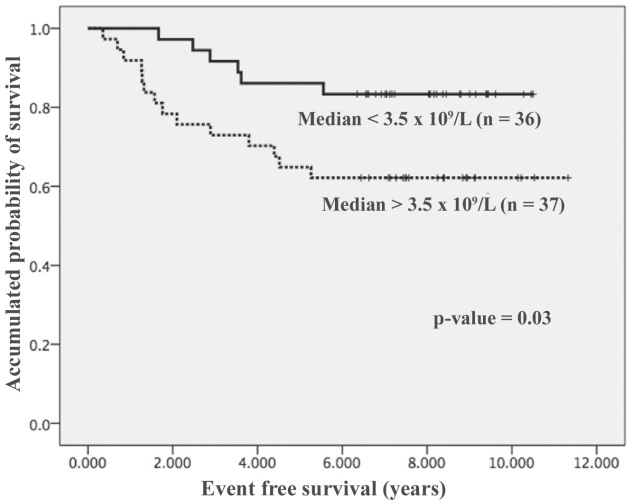

Figure 2 – Event-free survival (EFS) curves for children with acute lymphoblastic leukemia, according to Kaplan-Meier method. The vertical lines on the curves represent patients alive in first remission. The probability of EFS for patients with a median leukocyte count during the maintenance phase of chemotherapy below 3.5 x 10^9/L (n = 36) was 83.3% ± 6.2% and for those with a median above 3.5 x 10^9/L it was 62.2% ± 8.0% (n = 37; p-value = 0.03)

Analyses relating to prescribed doses of MTX are not available because there was no uniformity in the medical records regarding this variable.

There were no significant differences in the univariate analysis of EFS in relation to gender (p-value = 0.18) or the median neutrophil count (p-value = 0.74). Data regarding to the median neutrophil counts were available for 65 patients. The median neutrophil count ranged from 0.65 to 10.9 x 10^9/L (median: 1.65 x 10^9/L).

In the multivariate analysis for risk of relapse, three variables with p-values < 0.2 in univariate analysis were initially included in the Cox regression model: 6-MP dose, percentage of "appropriate" interruption of chemotherapy (according to the protocol) and median leukocyte count. Patients with higher risk of relapse were those who had scores of interruption of chemotherapy below 2%, presenting a risk of relapse 4.9 times higher than those with interruption above 2% (p-value = 0.001). Children who had leukocyte counts above the median of the total group had a 2.5 times higher risk of relapse than those with counts below the median (p-value = 0.066). The 6-MP dose was excluded from the model because it failed to be statistically significant when the model was adjusted for the other two variables.

Discussion

The excellent results obtained in the treatment of childhood ALL have been attributed to advances in chemotherapy and supportive treatment and to the improved understanding of the disease's biology and immunology. However, in order to achieve this success rate, just choosing

an excellent therapeutic scheme is not enough. It is essential that there is an adequate infrastructure, availability of drugs and that the team, consisting of doctors, nurses and other professionals, is motivated and trained to follow the proposed protocol.[4] Moreover, adherence to treatment protocol by the child/parents or guardians is essential.[5,6]

Adherence to treatment protocols by physicians is also important, but this is rarely assessed in the literature.[10] Inappropriate medical prescriptions should be considered one factor that may affect response to chemotherapy and therefore the prognosis of patients with ALL.[8,11]

This question was already evident in studies by British researchers who reported significant improvement in the prognosis of children with ALL treated with the UKALL VIII protocol when compared to earlier schemes. The improvement was attributed to the creation of stricter rules in prescribing 6-MP and MTX during the maintenance phase. Although the doses recommended in previous protocols were similar to those of UKALL VIII, there was no defined line for the adjustment of doses and there was a trend towards the use of quantities that would not cause "deep" marrow toxicity.[12,13]

Several authors consider that the intensity of maintenance chemotherapy is one of the determinants of EFS in patients with ALL.[14] The leukocyte count would be an indirect way to evaluate this intensity. Elevated leukocyte counts may be associated with too little exposure to adequate concentrations of 6-MP and/or MTX during the maintenance phase of treatment[15] and hence with a greater likelihood of relapse. In this study the median number of neutrophil and leukocyte counts for the entire group was higher than the counts outlined in the protocol and, in the univariate and multivariate analysis, the subgroup with a mean leukocyte count above the general median during maintenance had an EFS curve lower than that of the subgroup with scores below the median. The induction and maintenance of a "controlled" leucopenia within the limits of clinical tolerability may have contributed to a better prognosis for the subgroup.

Another indirect way of retrospectively assessing the intensity of chemotherapy would be the need for interruptions during maintenance due to signs of myelotoxicity or organ dysfunction. We observed the following in this study: a higher percentage of days with "appropriate" chemotherapy interruptions, that is, in accordance with the protocol, because of significant organic toxicity during the maintenance phase, was related to a favorable outcome. This seemingly paradoxical observation may be explained by the following hypothesis: the absence of those signs of toxicity for prolonged periods - and therefore with less days of suspension of chemotherapy - could be a result of insufficient systemic exposure[16,17] due to: i) the prescription by physicians of doses below the ideal therapeutic range for that patient, since it is known that there is great variation in the individual metabolism of 6-MP and MTX causing the "recommended" doses in the protocol to be sometimes insufficient and sometimes excessive for patients and ii) failure to comply with treatment by patients/caregivers.[18] In this study, it was not possible to determine the relative contribution of each factor in increasing the likelihood of relapse, as this would require a prospective design and diversified methods to measure noncompliance.

Currently, tools are available to assist in optimizing the therapeutic regimen[19-21] in addition to indirect measures such as leukocyte and neutrophil counts. These tools include the identification of individuals with inherited low TPMT activity; this would make it possible to adapt and individualize 6-MP doses while maintaining treatment efficacy and minimizing toxicity hazards.[20,21] Noncompliance can also be monitored by this method.[9,22]

Thus, the literature and our results show that we must seek to prescribe the maximum dose tolerated by the patient, ensuring proper exposure to chemotherapy. For this, "forcing" the patients' tolerance may be required, even when leading to occasional chemotherapy interruptions, within limits, with no compromise to drug exposure and no violation of protocol guidelines.

Note that about 20% of patients experienced undue interruption of chemotherapy as guided by physicians at least once. A study conducted in 1995 by the same researchers found that such behavior occurred in 40% of children (unpublished data) and thus showing a significant improvement, but there is still insufficient understanding of the need to "force" patients to the highest tolerable doses of 6-MP and MTX during the maintenance phase. In a study conducted in Indonesia, 49% of doctors and nurses interviewed reported that, at least "sometimes", they failed to strictly follow the recommendations of the treatment protocol.[8]

The institution where this study was carried out is a state facility and serves patients with low socioeconomic and cultural statuses, many living in distant locations. Therefore, it is possible that doctors sometimes avoided increasing doses of chemotherapy to the highest tolerated dose during the maintenance phase as recommended in the protocol, or delayed the administration of chemotherapy, fearing complications or because they had concerns regarding the understanding and adherence by the patients' relatives.[3,23] In developed countries, where such difficulties probably occur less frequently, concerns with adherence by physicians to treatment protocols are also relevant. British researchers found in an audit of the medical record notes of ALL patients that 30% of the results of leukocyte count and oral doses of chemotherapy were not recorded during the maintenance phase. Additionally, adjustments in doses of 6-MP and MTX were considered inconsistent according to protocol guidelines in 7.4% of cases. These authors developed a support system (web-based decision-support system) for decisions when adjusting the doses of medications and found that in 26% of cases when the system was not used, the doses were not adjusted in agreement with the rules defined by the treatment protocol.[24]

It is unlikely that there is only one reason why doctors and health professionals fail to properly follow the protocol guidelines.[10] In a study by Sitaresmi et al.,[8] 11% of physicians and 17% of nurses admitted to not following protocol recommendations simply because they did not know them. In addition, a small number cited forgetfulness and busy schedules as reasons for noncompliance.

The main limitations of this study relate to its retrospective nature and the relatively small number of cases. The data recorded in the records were sometimes incomplete making it difficult to clearly understand the reasons why the protocol guidelines had not been strictly followed.

The treatment of ALL, similar to other malignancies, is complex and response to therapy depends on several factors. The findings of this and other studies suggest that the possibility of noncompliance to protocol, be it by patients and family or by physicians, should be included in the evaluation of ALL treatment failure and that rigorous monitoring of treatment protocols by doctors and patients certainly contributes to a more favorable prognosis.

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