Abstract

Objective: To evaluate compliance in children with acute lymphoblastic leukemia.

Method: Compliance was assessed through specific interviews.

Results: A total of 73 patients, aged under 18 and who had concluded the maintenance phase of chemotherapy, were enrolled on the study. Eighty-one per cent of the interviews were conducted with the patients’ mothers; 92% of the families stated that medical instructions had been understood well. Interviews indicated that 27% of the patients did not receive their medication twice or more during the maintenance phase, without medical direction for this. These children were considered non-compliant. Sixteen per cent of the children failed to receive their medication three times or more. The main reason for non-compliance was forgetfulness. In ten cases the reported dosage of drugs was not that which was prescribed. No significant associations of non-compliance with parents’ schooling level, number of family members or per capita family income were detected. The 8.5-year estimated probability of event free survival was 72.4% (95% CI: 59.2-82.3). The event free survival curves for non-compliant children were not statistically different from those for the compliant group.

Conclusions: Results suggest that comprehensive approaches to the problem of non-compliance are urgently needed.

Original Article

Introduction

Acute lymphoblastic leukemia (ALL) is the most common neoplasm during childhood. Over the last 30 years, there has been a significant improvement in the prognosis of children with ALL. Currently, 70 to 80% of recently diagnosed children in developed countries present prolonged disease-free survival, with the majority of them being cured. Despite this progress, even at services with high rates of cure, around 25% of children still suffer relapses of the disease.

One of the possible explanations for observed differences in survival and duration of remission in children suffering...
from ALL, treated with similar chemotherapy regimen, could be inadequate use of the medication prescribed.3

Therefore, undertaking studies to assess compliance with treatment as a factor that could affect the response to chemotherapy and, consequently, the prognosis of patients with ALL takes on great importance. Nevertheless, little published work has taken as its objective the study of compliance with treatment in children and adolescents with leukemia.4-16

This research project took as its primary focus the evaluation of compliance with treatment during the maintenance phase of chemotherapy in a population of children with ALL.

**Patients and methods**

The study population was made up of children suffering from ALL, aged less than 18 years, having undergone no previous treatments and who had reached the maintenance phase of the Brazilian therapeutic protocol GBTLI-93. Seventy-three patients who had been diagnosed and treated at the Hospital das Clínicas at the Universidade Federal de Minas Gerais (UFMG) between May 1997 and July 2001 were enrolled. The minimum follow-up period was 16 months and the maximum was 102 months (median, 57 months) by July of 2004. There were no follow-up losses in this sample. The characteristics of the population are summed-up in Table 1.

The chemotherapy maintenance phase was chosen for compliance treatment assessment because it is founded on the use of 6-mercaptopurine (6-MP) and methotrexate (MTX), with the first of these given daily by oral route, over a prolonged period and under the responsibility of the patients’ families. The 6-MP was given at an initial dose of 50 mg/m²/day via oral route, daily (maximum dose of 100mg/m²/day) and MTX was administrated intramuscularly, at an initial dose of 25 mg/m²/week (maximum dose of 40 mg/m²/week), both adjusted in order to maintain leukocyte counts between 2,000 and 3,000/mm³ and phagocytes above 500/mm³. The duration predicted for the maintenance phase was from 1 year and 6 months to 2 years. All patients had free access to medication.

In order that their socio-economic status could be assessed, patients’ families answered a questionnaire on the following details: patient identification, identification of people living at the patient’s residence, education, identification of people that work - profession, occupation and monthly individual income expressed in multiples of the national minimum salary (the family income per capita was calculated based on this information), description of place of residence, electricity consumption (consumption was calculated in KWh/day based on the electricity bill for the family residence) and supporting data such as feeding habits, leisure activities, cultural activities, family medical care and decision making within the family unit.

Treatment compliance was evaluated by questionnaire. Questions were on the following subjects: medication being taken by the child at the time that the questionnaire was applied, whether there was an adult responsible for administering medication, regularity of the time at which medication was administered, the number of occasions on which the patient did not receive 6-MP or MTX without having been directed to interrupt chemotherapy by the treating doctor, what procedure was adopted on such occasions, problems encountered with administering

**Table 1** - Characteristics of the population of children suffering from lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pacientes (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>30:43</td>
</tr>
<tr>
<td>Median (variation) of age on diagnosis in years</td>
<td>4 (1.2-16.3)</td>
</tr>
<tr>
<td>Median (variation) of leukocyte counts on diagnosis (x10⁹/l)</td>
<td>6.4 (0.7-374)</td>
</tr>
<tr>
<td>Median (variation) of the number of family members</td>
<td>5 (3-13)</td>
</tr>
<tr>
<td>Median (variation) of the <em>per capita</em> family income (minimal wage/month)</td>
<td>0.68 (0.16-41.3)</td>
</tr>
<tr>
<td>Median (variation) of the educational level of the person responsible for medication (school years)</td>
<td>7 (1-15)</td>
</tr>
<tr>
<td>Number (%) of children with pre-B leukemia CD10⁺</td>
<td>47 (74%) *</td>
</tr>
</tbody>
</table>

* Immunophenotyping was performed in 63 out of 73 cases.
Compliance in children with acute lymphoblastic leukemia – de Oliveira BM et alii

Results

Analysis of the questionnaires on the 73 patients enrolled on the study revealed that in the majority of cases (81%), the mother was the informant, 96% of the patients reported using 6-MP; 84% of the patients received their medication at night, 92% of the patients had understood their physicians’ instructions well and their doubts, when there were any, were related more to the disease than to information about the medication – times doses and side-effects – or to caring for the children. In 83% of the cases the mother was responsible for administering medication. In two cases it was found that none of the patients’ relatives was responsible for administering medication to the patient, and that not even the patients themselves were made responsible for the task. In these two cases compliance failures were detected.

When the criterion was defined as two or more occasions on which medication was not administered without medical instructions, non-compliance was present in 20 cases (27%). According to this criterion there were no associations detected between non-compliance with treatment and the education of the person responsible for medication, (p = 0.94), the number of family members (p = 0.75) or per capita family income (p = 0.75).

When non-compliance was defined as three or more failures to take medication, 16.4% of cases were non-compliant. This criterion also failed to demonstrate associations between non-compliance and the education of the person responsible for medication, (p = 0.14), the number of family members (p = 0.88) or per capita family income (p = 0.60).

The prime motive for non-administration (80% of cases) was “forgetting”, very often related to the performance of domestic tasks and religious and social activities. Motives related to the children themselves such as being asleep, “tantrums” or refusing to take the medication were less common. Other motives such as “the mother got drunk and didn’t take the patient to chemotherapy” or “did not understand the medical instructions” were also cited.

Seventy-seven of the interviewees stated the dosage of 6-MP administered to the patient for whom they were responsible. In 10 of these cases (14.9%), the dose stated did not match the dose that had been prescribed. In seven cases the dose administrated had been higher and in three cases lower than the dose indicated.

Twenty-two (30%) medical records contained notes referring to the interruption of 6-MP and/or MTX with no medical instruction to do so, irregular use of 6-MP and the use of lower or higher 6-MP doses than those prescribed. Six of these patients also exhibited compliance failures as detected by the questionnaires.

Eighteen of the 73 patients suffered a relapse of the disease. Thirteen of these 18 children died. Deaths were the result of complications related to relapse. A similar proportion of relapses were observed for both groups of patients. The group of 20 children with compliance failures included five relapses. The group with no compliance failures (n = 53) contained 13 relapse cases. The estimated probability of EFS for the entire sample at 8.5 years of age was 72.7% (95% CI: 59.2-82.3). Global survival to 8.5 years was 81.1% (95% CI: 69.5-88.6).

According to the criterion of two failures to administer drugs with no medical instruction, no statistically significant difference was observed in EFS between compliant and non-compliant patients. Event-free survival was 72% (95% CI: 54.7-83.7) and 72.8% (95% CI: 46-87.8) for the two groups, respectively (p = 0.88). When the criterion of three missed medication administrations was used, no significant difference was observed in survival between the non-compliant and compliant patients. The estimated probability of EFS to 8.5 years of age was 75% (95% CI: 40.8-91.2) and 72.1% (95% CI: 40.8-91.2), respectively (p = 0.89). When the group of six children who exhibited compliance failures detected by questionnaires and by medical record notes was compared with the rest of the sample, an EFS probability of 66.7% (95% CI 19.5-90.4) was observed for the first group and of 72.9% (95% CI: 58.3-83.1) for the second group (p = 0.68). The EFS actuarial curve for these two groups is represented in Figure 1.
Compliance with treatment is a complex and multifaceted subject that performs an important role in clinical practice and medical research. Non-compliance with treatment can manifest in a number of different ways. The most common is the omission of doses. Notwithstanding, it can also be observed in the form of not acquiring medication, the use of incorrect dosages, inadequate intervals between doses and premature treatment interruption.18

When remission is achieved, children suffering from ALL become practically asymptomatic and often continue on prolonged and complex treatments. Against this background, compliance failures are, to a certain extent, to be expected.4 When they are not detected, such failures can increase the chances of disease relapse,3 resulting in incorrect assessments of chemotherapy efficacy.6

Assessment of compliance with treatment can be performed by direct methods (assaying medication levels in biological samples) or by indirect ones (reports by patients or their parents, physicians’ estimates, counting pills, etc.).19

Holding interviews with parents and patients (“self-reporting”), is the most widely used method in clinical practice. This type of assessment can make use of questionnaires, semi-structured interviews or less formal conversations.20 Interviews and questionnaires are considered an easily applied, low-cost method and also permit the pattern of compliance failures and the reasons for which they occur to be assessed. The primary limitation to the use of “self-reporting”, as a method for assessing compliance is that it tends to overestimate it.21 In the current study, the frequency of compliance failures may well have been underestimated since self-reporting of disobedience to medical prescriptions is, generally, more trustworthy than of obedience.

Physicians’ estimates are considered an imprecise measure of compliance with treatment, since they tend to overestimate it.19 In the present study, reports of incorrect medication use were found on 30% of medical records. This included patients who continued to take medication even when directed to stop by their doctors and also those who described using higher doses than prescribed, which undoubtedly increased the observed number of non-compliant patients.

Studies found in published literature used a variety of methodologies to assess compliance, which makes comparison problematic. Nevertheless, the results observed for the present sample are similar to those of other studies, in which compliance failures were detected in 2 to 52% of cases.4-15 In a study that included 39 patients from this sample, compliance with treatment was assessed by three different methods.16 Compliance failures were detected in 53.8% of cases, 33% by questionnaire, 30.7% from notes on medical records and 16.6% by means of 6-MP metabolite assay. Twenty-one patients exhibited compliance failures detected by at least one of these criteria and eight by at least two of them.

International studies have demonstrated that the percentage of non-compliant patients was higher when adolescent patients were analyzed separately. The present study did not identify an association between patient age at the point of diagnosis and failures in compliance with treatment. Just six patients, however, in this sample were aged 10 years or more at diagnosis.
The great majority of interviewees reported that they had understood their doctors’ instructions well, with doubts, when there were any, relating to the disease. Despite this, it was found that approximately 15% of the patients were taking 6-MP doses different from those recommended by their treating doctors. There is consensus in the literature that compliance with treatment is greatly influenced by the perception that the patient and/or their parents have of the disease. For some researchers, patients will have a greater tendency towards compliance with treatment, if they believe that their doctor is correct, that the disease involves risk and that the treatment prescribed will reduce the risk of complications or death, or that their health will improve. It is important that information provided is clear, that there is no ambiguity and that patient needs be evaluated periodically.22

The primary motive for failures to administer chemotherapy was forgetfulness. This finding is compatible with other reports in the literature which have found that forgetfulness, worries and lack of medication were the motives most often cited by parents of cancer patients to explain medication compliance failures.6,23

The adequate level of treatment compliance needed to achieve a cure from ALL, or inversely, the degree of non-compliance that could result in disease relapse, is unknown.15 English researchers have suggested that a child with ALL should receive a minimum of 95% of the medication prescribed them in order to be considered completely compliant with treatment.3

No studies were found in the literature consulted that took as their objective the evaluation of the influence that compliance with treatment has on the prognosis in juvenile ALL. Even without confirmation that non-compliance influences the survival of these patients, there is much evidence that it can be one of the determinants of treatment response. Rates of remission achieved in developed countries and those in development can be similar, but the rates of relapse are much higher in the second category. A large proportion of these relapses take place during the outpatients phase of treatment.24,25 With certain communities and ethnic groups, it is difficult to convince family members of the need for continued treatment during the maintenance phase, when the children appear to be cured.7 These data suggest that other explanations, in addition to biological factors, are needed for the unfavorable progress of patients who live under adverse conditions. One hypothesis could be non-compliance with treatment.

The results of this study did not reveal any significant difference in EFS, when groups of non-compliant patients defined by two different criteria were compared with a group of compliant patients, irrespective of which criterion was used to define compliance with treatment.

It is important to point out that the number of patients in this sample was relatively small and that the criteria adopted to define non-compliance could have been excessively rigorous. Since non-compliance with treatment can be extremely prejudicial to ill children, we considered that the sensitivity of the methods used for assessing compliance was more important than their specificity. A balance between these parameters can be achieved with the use of more than one assessment method or criterion. Until safer measurements are available, it is recommendable that a combination of methods be used for assessing compliance.18,21

The information obtained through this study of several aspects related to compliance with treatment can be used to benefit patients, attempting to minimize the negative effects of non-compliance. It is unlikely that a patient will fail to follow medical instructions for a single reason. This being so, complex interventions that involve several techniques are normally required before satisfactory results can be obtained.26 It is essential that, when discussing strategies for improving compliance, professionals concern themselves with understanding and taking account of the reasons why patients and their families have not complied with treatment, what their wishes are, their personal priorities and social ties, in order to involve them in their own care and for them to participate in treatment decisions, which will undoubtedly contribute to better motivation and compliance with treatment.27

References