CHAPTER 5

Health-care providers' compliance with childhood acute lymphoblastic leukemia protocol in Indonesia

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ABSTRACT

Background
Non-compliance with childhood acute lymphoblastic leukemia (ALL) protocol is an important determinant of poor treatment outcome. Non-compliance with protocol may not only concern parents or patients, but may also concern health-care providers (HCP). Our study examines the accuracy of leukemia risk classification and attitude of HCP toward protocol compliance in Indonesia.

Procedure
A combined retrospective study of medical records (MR) and a cross-sectional questionnaire study with HCP were conducted. Accurate ALL risk classification in MR was assessed. HCP’s knowledge of risk classification and their attitude toward protocol compliance were examined.

Results
A total of 164 MR patients with ALL were assessed and 97 HCP were interviewed. The protocol criteria for high-risk were not complete in 82 MR (50%). Of 97 HCP, 95% did not mention all 5 protocol criteria for high-risk. Both in the MR as well as in the questionnaires lymphoblast count on day 8 of chemotherapy, as early response to treatment, was the most frequently missed item (missing in 35% of MR and 85% of questionnaires). Only 14% of respondents actually checked with parents whether they administered the prescribed medicines.

Conclusions
Our study shows that HCP should improve their knowledge and assessment of childhood ALL risk classification, especially lymphoblast count on day 8 of chemotherapy. Proper risk classification and subsequent correct treatment may enable more children to be cured of leukemia.

Keywords: childhood acute lymphoblastic leukemia; health-care providers; compliance; protocol; developing country.

INTRODUCTION
More than 80% of children live in resource-limited countries, where survival rates of childhood acute lymphoblastic leukemia (ALL) are often less than 35% [1-5]. In contrast, recent survival rates in developed countries are about 80%[6]. Causes of treatment failure in resource-poor countries include delayed diagnosis, abandonment of therapy, death from toxicity caused by suboptimal supportive care, co-morbid conditions and non-compliance with therapy protocol which leads to an increased number of relapses [1,3].

Lacking compliance with treatment protocol is considered to be a major determinant of poor ALL treatment outcomes. This non-compliance may not be restricted to patients and parents, but may also concern physicians [7]. Prior studies did examine non-compliance of cancer patients [7-13], but few assessed non-compliance of health-care providers (HCP).

Precise diagnosis and risk classification are essential to successful treatment. This accurate assessment at diagnosis is needed to direct treatment, so that patients are neither under- nor over-treated [6]. Proper treatment compliance is an important prognostic factor. In order to comply, physicians must have appropriate knowledge of risk classification, knowledge of protocol prescriptions, and a positive attitude toward the importance to follow the protocol.

Our study examined the accuracy of leukemia risk classification as well as belief and attitude of HCP toward protocol compliance in Indonesia.

METHODS

Setting
Indonesia is a multi island state, and has a population of approximately 220 million of whom 37% are children under 15 years. Our study was conducted at the pediatric department of Dr. Sardjito Hospital in Yogyakarta, Indonesia. The hospital is both a teaching hospital of medical faculty of Gadjah Mada University, and a tertiary-care referral hospital of Yogyakarta and Central Java Provinces. Annually approximately 30-40 children are diagnosed with ALL. The pediatric department consists of a clinic (VIP, 1st, 2nd, and 3rd class) and a policlinic (VIP and general). VIP and 1st class patients can choose their own pediatric oncologist. The 2nd and 3rd class patients attend the clinic and general policlinic where they are treated by monthly rotating pediatric residents.

Residents have an important influence on success of treatment and cure of cancer patients because most patients are hospitalized at the 3rd class wards and visit the general policlinic. Nurses, having the closest contact with parents and patients, are essential contributors. Nurses rotate every 4-5 years in all wards.

Study design
This was a combined retrospective and cross-sectional study. The
A retrospective part consisted of a MR study of ALL patients. The cross-sectional study was conducted using a self-administered semi-structured questionnaire with HCP.

**Medical Records Study**

MR of childhood ALL patients diagnosed between January 1997 and August 2002 were abstracted. Patients were treated by the COM-ALL-92 protocol from 1997 until 1999, by the WK-ALL-99 pilot protocol from 1999 till 2000[14], and by the WK-ALL-2000 protocol until August 2002[15]. These protocols consist of various phases: 7 weeks induction, 6 weeks consolidation, 5 weeks re-induction (only for high-risk patients), 99 weeks maintenance. Physician adherence with protocol directions was analyzed. Assessment and documentation of bone-marrow punctures at diagnosis, type of risk classification and protocol assignment were noted. According to the protocol, there were 2 types of risk: standard-risk (SR) and high-risk (HR). Patients should be treated with HR protocol, if at least one of the following criteria is present: age <1 year or >10 years, leukocyte count >50,000/cmm at diagnosis, central nervous system or mediastinal mass involvement, and poor early chemotherapy response defined as presence of >1,000 lymphoblasts in peripheral blood on day 8 of chemotherapy. MR of all patients are kept in the same manner in the same storage that is maintained by trained MR staff and only accessible with special permission from hospital authorities. Laboratory results are both embedded in doctor notes and recorded on separate sheets in the MR. When information was missing in the MR, we also checked the laboratory records and special leukemia registration records.

**Questionnaire study**

This study was conducted through a self-administered, semi-structured questionnaire. The questionnaire was part of a larger questionnaire and more extensive research on compliance with childhood ALL treatment in Indonesia. All HCP working at the pediatric hematology-oncology department were contacted individually by the researcher and requested to complete the questionnaire at home or in the hospital. The questionnaire focused on knowledge of ALL risk classification, belief and attitude of HCP toward protocol compliance (Table I). Open questions were used to assess knowledge of risk classification. A semi-structured questionnaire was used to assess HCP belief of importance to comply with the protocol (2 items), attitude toward explaining importance of protocol compliance to the parents (6 items), attitude toward checking protocol compliance of parents (4 items) and reasons for not following the protocol (13 items).

We divided reasons for not following the protocol into 3 categories: appropriate protocol deviations due to side-effects or patients illness (2 items), protocol deviations due to resource limitations and non-compliance of parents (5 items) and protocol deviations due to non-compliance of HCP (6 items). Our questionnaire used a five-point Likert type rating scale (from strongly agree to strongly disagree and from never to always). To standardize the scale ranges and simplify interpretation, the scale ranges were converted to 0-100 with 0 indicating the lowest score and 100 indicating the highest score. A panel of Dutch and Indonesian doctors and psychologists assured appropriate, clear and coherent statements. The questionnaire was pilot-tested for its content, for the clarity of language and for cultural sensitivities on Indonesian HCP. A few minor adjustments were made on the basis of the pilot-test. Anonymity and confidentiality were guaranteed. The study was approved by the Medical Ethics Committee of Dr Sardjito Hospital.

**Data analysis**

Data management and analysis were performed by using SPSS for Windows version 12. Frequency distributions, means, standard deviations, and Cronbach’s alpha reliabilities were calculated for each scale. Chi-square test and one sample student’s t-test were used to measure the difference between doctor and nurses. Pearson correlations were used to correlate variables. Type 1 error (alpha) level was set at 0.05.

**RESULTS**

**Medical Records study**

Of 164 ALL patients who were enrolled in the study, criteria for high-risk were not complete in 82 patients (50%). Leukocyte count was not registered or checked in 2 children (1%). A chest X-ray was either not made or recorded in 13 children (8%). A lumbar puncture was not performed or not recorded in the MR of 44 patients (27%). Of the 164 patients, 21 refused the treatment and 14 received therapy with a duration shorter than 8 days due to death or drop out before day 8. Of the remaining 129 patients, no data was available on lymphoblast count in
peripheral blood at day 8 in 45 MR (35%). According to the protocol, the day 8 assessment is an important indicator of risk classification. In SR patients, if the absolute count of lymphoblasts on day 8 is more than 1000/mm³, the risk classification should be changed into HR. Consequently the classification as SR was not sure in these 45 cases. Of the 84 patients in which lymphoblast count on day 8 was determined, this was not actually carried out on day 8 in 51 patients (61%) and of 10 patients (12%) the exact date of determination was not given.

We found that 76 patients (46%) had SR-ALL and 88 patients (54%) had HR-ALL. All 76 SR-ALL patients were correctly diagnosed as SR-ALL. One of them, however, was treated according to a HR protocol. Of the 88 patients who should have been classified as HR-ALL patients, 9 were incorrectly classified and treated as SR. In addition, one other child was correctly diagnosed as HR, yet treated as a SR patient.

Questionnaire Study

From November 2004 until August 2005 all 135 HCP working at the pediatric haematology-oncology department were requested to participate in our study. A total of 102 providers (response rate 76%) participated and returned questionnaires: 4 pediatric oncologists (response rate 100%), 65 residents (response rate 78%), and 33 others (response rate 68%) consisting of 28 nurses, 2 hematology technicians, 1 hemato-oncology data manager, 2 psychologists. For our study on knowledge of risk classification and attitude toward protocol compliance, we excluded 5 HCP who do not need to have knowledge about risk classification and the protocol based on their profession (psychologists, hematology technicians and data manager). Reliability was assessed by calculating alpha coefficients. Cronbach alpha coefficients varied between 0.67 and 0.87 (Table 1).

Knowledge of risk classification

Respondents had little knowledge of risk classification. Only 5 of 97 (5%) respondents; 3 (4%) doctors and 2 (7%) nurses mentioned all 5 high-risk criteria of the WK-ALL-protocol. The lymphoblast count on day 8 of chemotherapy was the most often forgotten criterion. Except for the knowledge of lymphoblast count on day 8, doctors have significantly higher knowledge of risk classification compared to nurses (Table 2).

Attitude toward protocol compliance

The HCP’s beliefs about the importance of protocol compliance scored high, and there was no difference between doctors and nurses (Table III). Forty-nine percent of respondents mentioned that they, at least sometimes, do not follow the protocol precisely. The most frequently mentioned reasons for postponing the protocol were illness, side-effects, and lack of drugs (Figure 1).
More doctors deviated from the protocol due to side-effects or illness of the patients than compared to nurses (OR 3.2; 95% CI 1.2-8.6; p=0.01). There was no significant difference in protocol deviations due to non-compliance of HCP between doctors and nurses (OR 1.8; 95% CI 0.6-5.0; p=0.33) (table III). There was no correlation between protocol deviations due to non-compliance of HCP and knowledge of risk classification (r=0.01; p=0.99), belief about importance of protocol compliance (r=0.05; p=0.61), explaining to parents (r=0.14; p=0.17), and checking protocol compliance with parents (r=0.02; p=0.82). Doctors significantly more frequent explained the importance of protocol compliance to the parents compared to nurses (mean difference 13.4; 95% CI 5.1-21.6; p=0.002). Both doctors and nurses had low scores in checking the protocol compliance of parents (table IV). In total 45% of respondents assumed that parents always administer the prescribed medicines. Yet only 14% of respondents stated that they actually check with parents whether they administer the prescribed medicines. Seventy-five percent of respondents assumed that parents never alter the dosage of prescribed drugs due to side-effects. However, only 7% of HCP mentioned that they ask parents whether they alter the dosage of drugs because of side-effects.

**Table 3: Comparison belief and attitude toward explaining and checking protocol compliance of parents between doctors and nurses**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Doctor N=69</th>
<th>Nurse N=28</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beliefs about importance of protocol compliance</td>
<td>87±15</td>
<td>94±12</td>
<td>Ns</td>
</tr>
<tr>
<td>Explaining importance of protocol compliance to parents</td>
<td>73±18</td>
<td>59±19</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Checking protocol compliance of parents</td>
<td>39±23</td>
<td>35±18</td>
<td>Ns</td>
</tr>
</tbody>
</table>

*The scale was rescaled to a 100-point scale (0=the worst score, 100=the best score)*

**DISCUSSION**

Non-compliance with treatment is a complex phenomenon that heavily influences the outcome of therapy and may increase the probability of disease relapse [10,13,16]. Non-compliance with protocol can manifest in a number of different ways: missed diagnoses, incorrect assignment of protocol, omission of doses, inadequate doses, incorrect interval between doses and early interruption of treatment. Patients or parents may not be the only ones who fail to comply.

Physicians may also fail to comply with defined protocol requirements. On top of that, doctors have a strong influence on compliance of their patients.

Accurate diagnosis and risk classification at diagnosis are important to ensure that patients are treated according to the appropriate protocol. Our MR study found that in half of the MR not all 5 high-risk criteria were noted. The HCP knowledge of risk classification should be improved, since only 4% doctors and 7% nurses mentioned all 5 protocol criteria for high-risk classification. Measuring blast count on day 8 of chemotherapy was the most frequently forgotten criterion, mentioned by only 17% of doctors and 7% of nurses. Similarly, 35% of the MR had no data on blast count on day 8. Early response to chemotherapy is a very important prognostic factor of childhood ALL [17,18]. Forgetting to assess lymphoblast count on day 8 of chemotherapy, especially in otherwise standard-risk patients, could result in under-treatment. We also found that 9 out of 85 (11%) patients who were treated as SR should have been upgraded to HR. This may have contributed to a number of relapses (25%) described in our previous study [19]. At diagnosis it would be helpful to include check-lists of risk classification in MR.

**Table 4: Comparison reasons of protocol deviations between doctors and nurses**

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Doctor N=69</th>
<th>Nurse N=28</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects</td>
<td>34 (49)</td>
<td>4 (14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Patients illness</td>
<td>32 (46)</td>
<td>7 (25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Non-compliance of HCP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too busy</td>
<td>5 (7)</td>
<td>2 (7)</td>
<td>Ns</td>
</tr>
<tr>
<td>Lack of HCP motivation</td>
<td>14 (20)</td>
<td>3 (10)</td>
<td>Ns</td>
</tr>
<tr>
<td>Forget</td>
<td>5 (7)</td>
<td>1 (4)</td>
<td>Ns</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>8 (11)</td>
<td>5 (17)</td>
<td>Ns</td>
</tr>
<tr>
<td>Patients looked healthy</td>
<td>5 (7)</td>
<td>1 (4)</td>
<td>Ns</td>
</tr>
<tr>
<td>Not necessary</td>
<td>6 (9)</td>
<td>1 (4)</td>
<td>Ns</td>
</tr>
<tr>
<td>Resource limitations and non-compliance of parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of drug</td>
<td>31 (44)</td>
<td>7 (25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients refusal</td>
<td>18 (26)</td>
<td>3 (11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lack of financial</td>
<td>29 (42)</td>
<td>6 (2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lack of parent motivation</td>
<td>31 (44)</td>
<td>3 (11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Alternative treatment</td>
<td>18 (26)</td>
<td>1 (4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Chapter 5

Physician compliance with dosing and timing of chemotherapy has been associated with improved survival rates among children with ALL [11]. Bury et al (2005) found that 26% of administered 6-mercaptopurine doses were inconsistent with protocol prescriptions [20]. Forty-nine percent of our respondents mentioned that they sometimes interrupt or change treatment administration according to the protocol. Doctors said to deviate from the protocol due to side-effects and illness of patients more often than nurses. Appropriate protocol deviations are needed when patients suffer from severe side-effects or illness especially in maintenance phase. In general both doctors and nurses had high scores on protocol deviations due to non-compliance of HCP. However, an interesting outcome was that 11% of doctors and 17% of nurses admitted that lacking protocol knowledge was a reason for non-compliance with the protocol. Forgetfulness and busy schedules were mentioned by a few respondents as reasons for non-compliance. These results were similar to studies in parents which found that forgetfulness, lack of medication, busy schedules, and financial difficulties were frequent reasons for non-compliance [9,10,13,21-23]. Lack of drugs is a problem in Indonesia, especially lack of 6 MP, which is an important drug during the maintenance phase. This drug is not on the WHO list of essential medicines, but for unknown reasons not on the list of Indonesian essential drugs.

Both doctors and nurses had low scores of checking protocol compliance of parents. Forty-five percent of HCP believed that parents never alter or stop the prescribed medication dosage, yet only 14% actually asked parents whether they alter or stop the dosage. In addition, most HCP (75%) assumed that parents never alter the dosage of prescribed drugs due to side-effects. However, only 7% of HCP mentioned that they actually ask parents whether they alter the dosage of drugs due to side-effects. This result was similar to Miller's study which found that clinicians tend to over-estimate treatment compliance of patients and that clinicians' capability to recognize non-compliance was poor [24].

A limitation of this method is that the actual compliance may be lower than reported, since we used a self-reported questionnaire. This method is subjective to recall bias, social desirability bias, and may tend to over-estimate adherence [16,21]. This is especially a problem in the Javanese culture, in which it is considered impolite to criticize others.

CONCLUSION

Knowledge about the childhood ALL protocol, particularly the risk classification, needs to be improved in the population of caretakers we studied. HCP rarely checked with parents whether medication has been given according to schedule, the existence of non-compliance seems an almost unknown phenomenon. At diagnosis it might be helpful to include check-lists of risk classification in MR. Since residents treat the majority of ALL patients in the population we studied, better teaching and supervision of residents are necessary to improve their knowledge of, and compliance with, protocols. Proper treatment may enable more children to receive potentially curative treatment.

Reference List