CHAPTER 9

General discussion
INTRODUCTION

The aims of this thesis are to assess the problems of non-compliance and abandonment in childhood ALL after the implementation of the parental education program, donation of chemotherapy and a randomized intervention with a medication diary book. The studies focus on assessing the abandonment rate, factors associated to non-compliance and evaluation of a randomized intervention with a medication diary book in the treatment outcome of childhood ALL.

The questions asked in this thesis are:
1. How big is the problem of treatment refusal or abandonment? Which factors are related to treatment refusal and abandonment of childhood ALL in Indonesia according to the parental point of view? (chapter 2, 3, and 4)
2. How are the compliance and attitudes of health-care providers toward the childhood ALL protocol? (chapter 5 and 6)
3. What is the benefit of using a diary-book in the treatment outcome of childhood ALL? (chapter 7 and 8).

1. How big is the problem of treatment refusal or abandonment? Which factors are related to treatment refusal and abandonment of childhood ALL in Indonesia according to the parental point of view?

Treatment refusal or abandonment is still a major problem in our study population, the second most common reason of treatment failure (24%) after toxic-death (36%). This finding was similar to other studies in many developing countries. Arora et al found that the abandonment rate of childhood acute leukemia in developing countries varied from 16 to 50% [1,2]. Abandonment was related to socio-economic status and educational status of parents, travel time to the treatment-center and affordable, locally available treatment. Metzger et al found that treatment abandonment was the most common reason for treatment failure in Honduras, in which 23% of ALL patients abandoned treatment. It was associated with prolonged travel time to the treatment facility [2]. Another study conducted in Chennai, India also found that 41% of 135 childhood ALL patients abandoned treatment and 18% had toxic-death [3]. Twinning programs between public hospitals in developing countries and established cancer treatment centers elsewhere showed improvements on survival and decreased abandonment rate and toxic-death: The La Mascota program between the La Mascota Hospital in Nicaragua and the Monza Centre in Italy and Bellinzona, Switzerland have shown a decrease in treatment abandonment from 30% to 5% [4]. The International Outreach Program between Recife Hospital in North-East Brazil and St Jude Children Research Hospital, Memphis, USA showed a decrease in the abandonment rate from 16% (1980-1989) to 1.3% (July 1994 to March 1997) [5].

Previous studies based on expert opinions found that lack of finances, transportation, essential drugs and local medical facilities were the main contributors to abandonment [6-7]. Our exploratory study (chapter 2), in which families of children who abandoned treatment were interviewed, found that reasons for refusal or abandonment were complex. Most parents mentioned several reasons. Most parents (77%) mentioned that they had financial problems due to the child's illness and 60% of parents said that transportation to hospital was difficult, expensive and time-consuming. However, only few families reported that financial difficulties and transportation problems were the only reasons for dropout. Beliefs of ALL incurability, children experiencing severe side-effects and dissatisfaction with HCP who failed to perform lumbar punctures and bone marrow punctures were also important considerations.

Similar to other studies [8-12], parents of childhood ALL patients reported in our study (chapter 3) that their children suffered from psychological as well as physical side-effects during chemotherapy administration. Behavioral alteration was perceived as the most frequent side-effect, reported by 92% of parents. The frequency of side-effects was weakly correlated to non-compliance. This study, however; had a positive selection group since it only included 51 of 72 (70%) patients. Ten of the 21 non respondents dropped out, and 11 children died before being interviewed. The respondents in our study were therefore probably the more compliant patients. Our finding was similar to some studies reporting that side-effects may be important contributors to non-compliance [13].

The exploratory study (chapter 2) in which parents of patients who abandoned treatment were interviewed also found that 81% of patients who started treatment suffered from side-effects and most of them (58%) perceived the side-effects as moderate to severe. The most common and bothersome side-effect was behavioral alteration: children felt scared, frightened, and traumatized through the medical procedures, according to 66% of parents. Our study on HRQL in childhood ALL patients (chapter 4) showed that children of the 2-4 year-old group had significantly more problems in procedural and treatment anxiety subscales than...
children in older groups (44 vs 71 and 57 vs 86, p<0.05). The dynamic psychological and social development of 2-4 year-old children can be interrupted by a serious life-threatening illness, regular invasive examinations and hospital visits, interruption of school attendance or social activities, as well as family crisis. Therefore, a special approach regarding medical procedures for young children is needed to promote their normal development.

Other important side-effects were infections: 83% of parents of ALL patients who were still in treatment, reported that their children suffered from infections (chapter 3) and 35% of patients who abandoned therapy mentioned that their children suffered from infections, and these side-effects were one reason for abandoning treatment (chapter 2). It should be emphasized that infections are the most common cause of treatment-related death in resource-poor settings, where supportive treatment is limited and most patients are malnourished.

Poor nutritional status decreases tolerance of chemotherapy, is associated with altered metabolism of chemotherapy and increased infection rate, resulting in poor clinical outcome. Preventing and managing side-effects should be emphasized. HCP should have appropriate knowledge and skills to early detect and vigorously treat any complications that might arise. Adjusting the protocol based on patients’ conditions is recommended in life-threatening conditions. Improving education and skills of HCP as well as providing supportive care for treating infections is mandatory.

Regarding beliefs of ALL curability, our exploratory study (chapter 2) found that there were 2 different points of view. Parents who refused treatment or abandoned early perceived that ALL cannot be cured by chemotherapy. They believed that alternative treatments were more effective than chemotherapy. Their beliefs were based on “lay resources” such as stories or experiences of relatives, friends or other parents. Families were also exposed to advertisements that promise a quick and easy cure. Unfortunately, they went home immediately after diagnosis, before being exposed to the structured parental education program. In contrast, parents who abandoned treatment in later weeks initially believed and trusted the information given in the parental education program. However, after their child suffered from severe side-effects and having seen other ALL patients die after receiving chemotherapy they started to weigh the benefits and harms of chemotherapy. This was quite similar to the findings in the study of Klefens et al and requires a different approach for prevention. For the former group who did not start therapy, the PEP should be initiated immediately after diagnosis, or better yet, while the diagnostic-evaluation is in progress. It is important to conduct non-patronizing, careful and extended discussions when alternative medical treatment is proposed by parents or patients. It may prevent their refusal or abandonment of medical treatment to seek useless, usually expensive and harmful alternative treatments. Open communication and structured parental education are important to ensure cooperation and compliance with chemotherapeutic regimens and to prevent treatment abandonment. For the latter group, the PEP should be an ongoing process, with regular group meetings of professionals and parents or patients, to discuss their health-beliefs, fears, and experiences on the ward.

Some reviews found that HCP play an important role in patient compliance. Compliance will also improve when physicians meet the expectations and needs of the patient and family. We found that one of the reasons to drop-out (chapter 2) was dissatisfaction with their doctors due to failing to perform lumbar punctures (LP) and bone marrow punctures (BMP). It must also be considered that a traumatic LP with lymphoblasts in the cerebrospinal fluid at diagnosis can adversely affect the treatment outcome of childhood ALL. This poor outcome may be due to an iatrogenic contamination of the cerebrospinal fluid by lymphoblasts in the peripheral blood. Another possibility is due to under-treatment of patients, who were actually patients with central nervous system involvement, but were not identified caused by the presence of erythrocytes in the cerebrospinal fluid. Howard et al, 2002 found that performing LP by less experienced physicians increased the risk of a traumatic LP. It is strongly recommended that LP must be performed by experienced physicians especially at diagnosis when higher numbers of lymphoblasts are circulating in the peripheral blood.

We found that leg-weakness was the most severe side-effect perceived by parents (chapter 3). Leg-weakness may be due to procedures-related pain (LP and BMP), proximal myopathy, myelopathy, and neuropathy. In addition, we found that in the induction, consolidation, and re-induction phases, where LP were more frequently performed, children had worse scores of HRQL, on the physical health and pain subscales than in the non-intensive phase (chapter 4). Considering all mentioned conditions above, it is very important that childhood ALL should be taken care of by a pediatric oncologist, not by rotating residents, even with good supervision.

Treating adolescent patients needs special approaches. Adolescents are
known to be the worst compliers in the pediatric and adult age ranges. This may be related to their complex developmental stage. Adolescence is a period of significant physical and psychosocial changes. A diagnosis of leukemia during this period has a major impact on their psychosocial and physical development. An adolescent normally focuses on relationships with friends, gaining autonomy from family members, body image and planning their future. Cancer treatment abruptly interferes and complicates these typical trends. Hospitalization separates adolescents from their peers for long periods. Treatment will change their physical appearance (hair loss, skin changes and weight gain) when looking good or at least normal is tremendously important. Patients become increasingly dependent on their family. In adolescence confusion arises when responsibility is transferred from parents to the teenager. Frequently it is not clear who is responsible for the tablet taking, and parents and teenagers disagree on this subject. Poor communication between teenagers and parents, confusion and disagreement influence treatment compliance among the adolescent group. Our exploratory study (chapter 2) found that some abandonment decisions were made by adolescent patients themselves. They decided to stop treatment because they believed that chemotherapy cannot cure the disease but may even worsen their condition. Their belief seemed to be influenced by other similar-aged patients. They shared their experiences, feelings, and beliefs with their peer group. Some of their information came from overhearing the clinical round discussions. It is important that physicians do not discuss patients' condition in front of the patient or other patients. Adolescents may pick up certain aspects of the information and may not be able to put it in the right context. This may create fear and misconceptions among them and their peers. Psychosocial support and open communication between HCP and a peer group of patients may facilitate their coping with the disease and its treatment. Regular meetings in a peer group or with the parents group should be instituted.

2. How are the compliance and attitude of health care providers toward childhood ALL protocol?

Non-compliance is not restricted to patients and parents, but can also concern health care providers. Health care providers may not comply with the protocol in a number of different ways: incomplete diagnoses, incorrect assignment of protocol, not properly initiating treatment, incorrectly calculated doses and not implementing the protocol properly. Accurate diagnosis and risk stratification at diagnosis are important to ensure that patients are treated according to the appropriate protocol. Our medical records (MR) study (chapter 5) found that in half of the MR not all 5 HR criteria were noted. The HCP knowledge of risk stratification should be improved, since only 5% of HCP mentioned all 5 protocol criteria for HR stratification. 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. Forgetting to assess lymphoblast count on day 8 of chemotherapy, especially in otherwise SR patients, could result in under-treatment. We also found that 9 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. At diagnosis it would be helpful to include check-lists of diagnostic requirements and risk stratification in MR.

Physician compliance with dosing and timing of chemotherapy has been associated with improved survival rates among children with ALL. Bury et al. (2005) found that 26% of administered 6-mercaptopurine doses were inconsistent with protocol prescriptions. Forty-nine percent of HCP mentioned that they, at least sometimes, do not follow the protocol precisely. The most frequently mentioned reasons for postponing protocol were child's illness and side-effects (chapter 5). Keep in mind that appropriate protocol deviations are needed when patients suffer from severe side-effects or illness especially during the maintenance phase.

Other reasons for HCP to deviate from the protocol were lack of knowledge, forgetfulness and busy schedules. Limited opportunities for continuing education and lack of local mentors for many doctors in resource-limited countries may result in misunderstanding of the protocol and mimonitoring of patient compliance. In addition, HCP in these countries have a high clinical workload. They must take care of more patients, often with severe conditions, have an additional heavy administrative work load and should assist patients with psychosocial and economic needs.

HCP mentioned that lack of drugs and finances of parents were reasons for postponing administering according to the protocol. Lack of drugs especially 6 MP
which is an important drug during the maintenance phase, is a problem in many resource-limited countries. This drug is on the WHO list of essential medicines, but for unknown reasons not on the list of Indonesian essential drugs.

HCP play an important role in the extent to which the patients comply with the treatment. HCP’s own belief in curability of ALL and efficacy of treatment will also influence their compliance with the defined protocol. We found that only a few (10 of 102) HCP did not believe in the curability of ALL. However, a majority (59%) of them mentioned that most patients will not be able to complete treatment due to financial problems (chapter 6). If HCP expect that patients or parents cannot complete treatment, their own motivation may decrease and subsequently the compliance of patients and parents may diminish and lesser performance and treatment outcome evolve.

Some reviews found that good communication and a good relationship between HCP and patients or parents will improve compliance. We found that most (88 of 102) HCP believed that poor communication between patients, parents, and doctors decreases the outcome of childhood ALL patients. However, some (64%) HCP mentioned that they had difficulties in openly discussing the disease with parents and patients. Fifty-six of them (55%) are uncertain if they are able to create a climate in which questions can be asked by parents and patients. Communication with parents and patients, particularly toward poor families, is impeded by differences in status and social hierarchical structures according to 68 HCP (67%). Some HCP stated that less elaborate explanations about the disease and its treatment were given toward poor parents (60%). In developing countries the importance of HCP’s perceptions, beliefs, attitudes, and communication skills is frequently underestimated. Health-care professionals need to realize that their own expectations and subsequent behavior differ between families with poor versus prosperous socio-economic backgrounds. This difference may play a role in the large drop-out rate and low percentage of survival among less affluent patients.

Awareness must increase so that HCP themselves have an important influence on the compliance of parents and patients and thereby can influence treatment results and possible survival of children with ALL.

It is important for HCP to ask patients/parents in a non-judgmental, open-ended way to keep communication open: “How many mercaptopurine pills does your child take each day? When do you give it? How many doses were missed in the past week?” HCP are also recommended to verify whether patients and parents understood the information they received. Our study found that many (67%) HCP mentioned that they use medical vocabulary with parents and patients of which they knew parents and patients would not understand.

To combat poor compliance, HCP must identify non-compliance in patients so they can implement interventions. Direct questioning about compliance can improve compliance rates. Our study found that almost half (45%) of HCP 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. We also found that most (75%) HCP 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 because of side-effects (chapter 5). This result was similar to Miller's study in which was found that clinicians tend to over-estimate treatment compliance of patients and that the clinicians' capacity to recognize non-compliance was poor.

3. What is the benefit of using a diary-book in the treatment outcome of childhood ALL?

To decrease the abandonment rate and subsequently improve the survival rate, a program was instituted in January 2004 at Dr. Sardjito Hospital, Yogyakarta. It consists of a structured parental education-program (PEP) and donation of chemotherapy for all new ALL patients. In addition to this program, a randomized study by providing a medication-diary-book for assigned new ALL patients was conducted. Earlier studies on interventions to improve compliance and treatment outcome found that the interventions were complex and labor-intensive. It included various combinations of: education, counseling, reminders, self monitoring, reinforcement, family therapy and additional support or attention. We conducted a randomized study to evaluate the effectiveness of using a medication-diary book in the treatment outcome of childhood ALL. The control group received PEP and donated chemotherapy only; the intervention group received a diary-book in addition.

Providing a diary-book may be a contributing factor improving the survival of childhood ALL especially in limited-resource countries. Our study (chapter 7) found that a medication-diary book is useful to improve the EFS estimate in childhood ALL patients especially whose mothers had a high
educational level (same or higher than senior high school). However, for parents with a lower educational level, there was no difference in the EFS estimate between the diary book group and the control group. Even though we designed the medication-diary books as simple and easy to be filled in, for mothers with a low education level it may be difficult to fill in the diary.

We also evaluated the use of diary (chapter 8). Forty of 91 (44%) distributed diaries were collected and analysed. This group may not be representative for the whole diary population. Furthermore, the majority of the parents of the collected diaries were higher educated, there is thus probably selection bias. We found that the individual use of the diary differs a lot. One diary was only used as a drawing book and another one was used to notice medication but also as a drawing book. Five diaries contained only medication, control and check marks, without any comments. The rest of the diaries contained marks and comments. This may be explained by the difference in education levels. As about 12% of the Indonesian population is officially illiterate and a higher percentage has probably hidden analfabetism, some parents may have not been able to fill in the diary. The group of collected diaries consist thus presumably of literate parents and it can be supposed that diaries are only suitable for higher educated persons. Probably more of the low educated diaries were not retrievable.

In spite of the probability of selection bias, we found that the mean total compliance to fill the diary for daily medication (dexamethason and 6 MP) was 74%±29% and median 86% (ranged: 0-100). The mean compliance to fill the diary for weekly medication (MTX per oral) was 48%±41 and 66%±56 in maintenance 1 and maintenance 2 phase, consecutively. This can be explained by the frequency of intake. Patients are more compliant when the frequency of intake is daily as opposed to weekly.

The diary-book could be used as an information source regarding treatment compliance, symptoms and other important problems during the treatment. Families were encouraged to write voluntary comments such as symptoms, laboratory results, procedures, and other important information. We found that the most frequently mentioned procedure was blood transfusion mentioned written in 17 (42%). This showed that most patients suffered from anemia and severe thrombocytopenia due to the disease itself or side-effects of chemotherapy. Fever and diarrhea were the most common symptoms reported in the diary. This information is important since these conditions may be the initial symptoms of an infection that leads to toxic-death. In our previous study, we found that treatment-related death was the second cause of treatment failure, in 23% of the patients. Early recognition and treating this infection may possibly prevent and reduce mortality.

Noteworthy comments from the diaries revealed things going wrong during ALL therapy: postponing the treatment due to unavailability of drugs and rooms, common barriers of therapy in developing countries. We encouraged parents to bring the diary during hospital visits in order to be checked by health care providers. By checking the diary regularly, giving good comments and instructing how to use the diary-book, parents are stimulated to use the diary. Some studies found that positive reinforcement when performing expected behaviors is an effective behavioral strategy to improve self management. It is known that people have a bigger tendency to use or do something when it is often repeated to them. Unfortunately, this checking was rarely being done. HCP need to be instructed to do this. Probably a check list at the policlinic can be helpful. It should contain items that should be asked at every visit, such as: Can I see your diary? Did you have difficulty in filling the diary? How many mercaptopurine pills does your child take each day? When do you give it? How many doses were missed in the past week? Did you have any fever? For parents with a lower educational level, the diaries should be made simpler, and more support and education is necessary to help them use it.

RECOMMENDATIONS FOR BETTER SURVIVAL OF CHILDHOOD ALL PATIENTS

1. At the diagnosis, a check-list of risk classification in medical records is needed to ensure that patients are treated according to the appropriate protocol.
2. Since the majority of ALL patients are treated by residents, better teaching and supervision of residents are necessary to improve their knowledge, skills and attitudes as well as their approach toward and communication skills with childhood ALL patients and their families. Improvement of supportive care is needed to prevent toxic-death.
3. LP especially at the diagnosis and BMP should be performed by skilled HCP (pediatric oncologists).
4. A structured parental education program should be provided as an integral part of care and it should be provided continuously during the treatment.
5. Psycho-social support for parents and patients should be provided.
6. A medication-diary book is important for compliance and cure. It should be made simpler. One consistent-nurse should regularly check the use of the diary and give instructions about how to fill it in during hospital visits.
7. Medication and room availability should be guaranteed. Government insurance should be continuously and include all chemotherapy and supportive treatment.

FUTURE RESEARCH
1. Medication diary-book research. Our study found that the compliance in filling the diary-book was quite good. The diary-book could be used as an information source regarding treatment compliance, symptoms and other important problems during the treatment. We also found that the medication-diary book improved the EFS estimate in patients whose mothers had high educational levels. Further studies should include more patients and longer follow up is needed.

2. Health Related Quality of Life research. Longitudinal study on HRQL is necessary to evaluate HRQL as an indicator of treatment outcome and predictor of compliance.

3. Contributing factors of treatment outcome.
   a. Assessment of the protocol
   Most patients died during the induction-remission. This may be due to the disease itself, especially because most patients have a more advanced disease at diagnosis or this may be due to the fact that the used protocol is too toxic. Assessment of the protocol is recommended.
   b. Diagnostic procedure.
   Accurate diagnosis and risk stratification at diagnosis are important to ensure that patients are treated according to the appropriate protocol. A precise diagnosis even at the molecular level is more important in developing countries so that resources are not wasted on inappropriate treatment.

Reference List
Chapter 9


Chapter 9


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