CHAPTER 1

General Introduction
INTRODUCTION
Of all the children worldwide, more than 80% live in developing countries. Improvement of the treatment of common fatal illnesses, like diarrhea and pneumonia has been achieved. Consequently, cancer will become a more significant cause of childhood mortality in developing countries. In developing countries, the 5-year survival rate of acute lymphoblastic leukemia (ALL), the most common malignancy in children, is often less than 35%\(^2\). In contrast, it has improved in recent years to about 80% in more developed countries\(^3\).

Causes of treatment-failure in resource-poor countries include treatment refusal or abandonment, death from toxicity and non-compliance with treatment protocol which lead to increased number of relapses. In many low income countries, treatment refusal or abandonment, the worst level of non-compliance, is the main reason of treatment failure. It is a complex problem, almost unknown in developed countries. In the developed countries treatment failure is mainly determined by relapses. Toxic death is a minor contributor.

In resource-poor countries high number of treatment failures is closely related to poverty and low educational standards. Lack of finances, transportation, essential drugs and local medical facilities were found to be main contributors to abandonment\(^4,5\). Limited knowledge and lack of awareness and recognition of the disease by both parents and health-care providers in rural areas may result in patients having a more advanced disease at diagnosis. These patients need more extensive treatment which requires more extensive and expensive supportive care facilities. Most patients have co-morbidities with malnutrition or recurrent infections. All these factors contribute to a high rate of toxic-death\(^6\).

Our previous medical records study found that treatment refusal or abandonment was the most common cause of treatment failure in Yogyakarta, Indonesia, where 15% of patients refused or abandoned treatment. There were significant differences in abandonment rates between poor and prosperous patients and between patients having low, intermediate or high education. We found that poor patients received less individualized attention from oncologists and less structured parental education. Most poor patients could not afford treatment and access to donated chemotherapy was inadequate\(^7\).

Our current study showed that 35% of patients refused or abandoned treatment. Similar to other chronic diseases, such as asthma, tuberculosis, and epilepsy, non-compliance with self-administration and prolonged treatment is a problem. Non-compliance rates for many long-term drug treatments were estimated to be more than 50%-60%\(^8-10\). Non-compliance with protocol is associated with poor outcome, increased chance of relapse, and results in incorrect assessment of chemotherapy efficacy\(^11,12\). Patients or parents may not be the only ones who fail to comply. Health-care providers (HCP) may also fail to comply with defined protocol requirements\(^13,14\). On top of that, doctors have a strong influence on compliance of their patients.

NON-COMPLIANCE AND ABANDONMENT OF TREATMENT
Definitions and problems of treatment non-compliance and abandonment
Compliance or adherence is the extent to which a patient's behavior coincides with medical or health recommendations given by health-care providers\(^15,16\). Compliance to medication is determined by the patient's perception of the risk compared to the benefits of the medication. Non-compliance is not restricted to patients and parents, but can also concern HCP.

Non-compliance of patients ranges from sporadic lapses to total withdrawal. There are different types of non-compliance: treatment refusal, treatment abandonment and loss of follow-up. Treatment refusal is defined as rejection of any therapeutic intervention after diagnosis is made, and abandonment as failure to complete prescribed therapy once it has begun. Loss of follow-up refers to missing subsequent appointments once treatment has been completed\(^17\). The patient who is lost of follow-up may have a relapse or may have even died at home. Treatment refusal or abandonment is widespread across developing countries. The abandonment rates of ALL vary from 16-50%\(^18\). It is the main reason of treatment failure in developing countries.

HCP may not comply with protocol in a number of different ways: incomplete diagnoses, incorrect assignment of protocol, not properly initiating treatment, incorrect calculating doses and not implementing protocol properly\(^19\). Non-compliance with prescribed drugs becomes an increasingly important issue in treating childhood ALL. Since self-administration of oral chemotherapy for a long period is required, it has become consistently apparent that patients do not take medication completely\(^20\). Childhood ALL is universally treated according to defined protocols. After achieving complete remission, ALL patients must take oral medication for at least 2 years of treatment to prevent relapse. Similar to other chronic diseases, such as asthma, tuberculosis, and epilepsy, non-compliance with prolonged treatment is a problem. It is illogical to assume that ALL patients,
regardless of the life-threatening disease, will really take the medication daily for 2 years especially because they are in relatively good health after achieving complete remission and suffer no immediate consequences when doses of drugs are missed.

Studies estimate that even in developed countries 10 to 40% of young children and 50 to 60% of teenagers with ALL on oral maintenance chemotherapy do not reliably take all their pills. Non-compliance may be one of the reasons why the outcome for teenagers with leukemia is worse than for younger children where other risk factors are the same. In developing countries, where the abandonment rate is high, the compliance of patients who do not abandon and presumably take their medication is really dubious, and might be worse. This may add to the number of relapses.

**Consequences of treatment non-compliance and abandonment**

Non-compliance with medication can substantially alter the outcome and also may lead to incorrect assessment of therapy efficacy. This erroneous conclusion may result in unnecessary diagnostic testing, hospitalization and changes in dose or regimen. It also increases costs of treatment due to increased physician visits and hospitalization rates. In clinical trials, non-compliance may result in misleading results, inconsistent response rates, and potentially erroneous dosing recommendations. Poor compliance can also break down the patient-doctor relationship, because of misconceptions about the effects of therapy, and prevent accurate assessment of the quality of care.

Since treatment regimens used for ALL are given for curative rather than palliative intent, compliance with chemotherapy for ALL patients is considerably important. Maintenance therapy for ALL is considered to be essential for long-term, disease-free survival, and non-compliance with maintenance chemotherapy seems to increase the risk of relapse. Lilleman et al found that ALL patients on maintenance treatment who have lower than average concentrations of intracellular metabolites of mercaptopurine and methotrexate had significantly higher risk of relapse, even after adjusting for other prognostic factors. Low concentrations of these drugs may be due to individual genetic variability influencing the accumulation of metabolites or inadequate medication compliance of patients (missed the drug, taking the drug in the morning or with milk) or non-compliance of HCP (not adjusting the dose according to low or high leukocyte count) or a combination of these factors. It is recommended to separate the timing of taking mercaptopurine and drinking milk, because intake of cow's milk may reduce the bioavailability of mercaptopurine. An evening schedule should also be recommended for oral mercaptopurine. Another important issue in ALL non-compliance is erroneous dose escalation in patients who appear "tolerant", yet in reality are "non-compliant" with chemotherapy. This can be dangerous: when these children suddenly do comply and take an inflated dose of medicine, severe myelosuppression may occur.

In developing countries, treatment refusal and abandonment are the most important factors influencing the survival rate of childhood ALL patients. It is the most common cause of treatment failure. The outcome of childhood ALL could be improved by interventions which reduce or prevent treatment refusal and abandonment.

**Factors of non-compliance and abandonment in ALL patients**

Non-compliance with medication is a complex and multifaceted phenomenon. It depends on many factors and no simple explanation for non-compliance can be established. The factors of non-compliance may be found in different areas: health-care providers, patients or families and treatment.

**Health-care providers' factors**

HCP play an important role in the extent to which patients comply with the medication. HCP own belief in curability of ALL and efficacy of treatment will also influence their compliance with the defined protocol. Good communication and relationship between HCP and patients or parents will improve compliance. Compliance will improve when HCP are able to communicate clearly about the nature of the disease, the possibility and anticipation of side-effects, and the importance of treatment compliance. HCP must provide clear and specific instructions. HCP are also recommended to verify whether patients and parents understood the information they received. It is also 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? Do you give it with food or drink? How many doses were missed in the past week?” Compliance will also improve when physicians meet the expectations and needs of the patient and family, show interest in the patients and if they meet the physician frequently.
HCP may also fail to comply with the defined protocols. Precise diagnosis and risk stratification are essential to successful treatment. This accurate assessment at diagnosis is needed to treat patients, so they are neither under- nor over-treated. Cure of ALL requires delivery of a complex and prolonged regimen of chemotherapy, and assiduous supportive care. Implementation of this care is best accomplished by following a protocol that lists diagnostic requirements, defines risk stratification, specifies chemotherapy drugs, doses, and schedules, and provides guidelines to optimize supportive care. To comply with the defined protocol, HCP must have adequate knowledge regarding proper implementation of diagnostic and therapeutic procedures.

Patients and families' factors

Age of patients

Adolescents are known to be the worst compliers in pediatric and adult age ranges. It 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 teenagers. Frequently it is not clear who is responsible for the tablet taking; parents and teenagers disagree on this subject. Poor communication between teenagers and parents, confusion and disagreement influence treatment compliance of the adolescent group.

Socio-economic status of families and patients

Socio-economic status is an important factor of treatment abandonment in developing countries. Patients with poor socio-economic status tend to have greater difficulty attending scheduled appointments and complying with protocol. Lack of transportation hinders poor families to attend the clinic and lack of finances prevents following the protocol. Prolonged and expensive treatment of childhood leukemia cannot be afforded. In addition, when a child has leukemia, the family generally falls back into a lower socio-economic class as treatment is expensive and parents are not able to keep their job or social position.

Education level of families

Education will influence income, knowledge, understanding and coping with disease. Lower levels of parental education adversely affect health seeking behavior, adherence with therapy and subsequent cure or survival from childhood leukemia. Especially the education of the mother is important. In educated families the ability and willingness to comply with the extended chemotherapeutic regimen may be higher.

Patients’ or parents’ belief about the disease (severity and prognosis), and effectiveness of treatment will influence treatment compliance. Patients who perceive their disease as serious, and who believe that the treatment will be effective and the disease can be cured are more likely to comply with their treatment. Locus of control is also associated to compliance. Compliance is greater in parents and patients who believe they have some control over their health (internal locus of control), compared to those who believe health is beyond their control (external locus of control). Outcome expectations may also influence treatment compliance. Non-compliers tend to focus more on immediate consequences than delayed consequences. Side-effects of chemotherapy tend to be immediate, whereas beneficial effects are realized only after a long period. In addition, when doses of drugs are missed, this will not immediately cause the symptoms of the disease to return, but it will affect long term prognosis.

Health-related quality of life (HRQOL) of patients

Treatment compliance and HRQOL are two distinct concepts. However, they are both related to the patient and need important consideration when assessing treatment outcomes. As the treatment for childhood ALL can be aggressive and associated with acute and long-term morbidity due to side effects, HRQOL is considered to be an important outcome measurement. Compliance and HRQOL are related to each other. Patient compliance with treatment is an important factor for the success of medication, and it will influence HRQOL. HRQOL during treatment is an important parameter for compliance. It may also influence compliance. During treatment, if HRQOL of patients goes down, patients...
or parents may become non-compliant. Implementing HRQOL measurements in pediatric health-care settings can improve communication between patients and HCP, increase patient/parent satisfaction with HCP, identify hidden morbidities, and assist in clinical decision-makings.

**Treatment's factors**

Length, complexity, and side-effects of treatment will influence treatment compliance. When drug regimen are more complex (more frequent, more doses, more drugs), and therapy requires a long period, compliance may decrease. Frequency, severity and type of side-effects of medication may influence compliance, however the evidence is conflicting. Some studies and reviews reported that side-effects may be an important cause of non-compliance. Other study found different results.

Treatment for ALL is long, complex and has side-effects. During chemotherapy, childhood ALL patients suffer from psychological as well as physical side-effects. The treatment requires carefully scheduled multi-drugs and expensive chemotherapies, many visits to hospital, and frequent blood counts to adjust the dose. Treatment is also intensive and toxicity results in a high frequency of infections and other complications of drug-induced bone-marrow failure. These complications lead to children spending more time in hospital and increase the costs due to expensive antibiotics and supportive treatment.

Availability of medication is an important factor of non-compliance, especially in countries with limited resources. Mercaptopurine, an essential drug for maintenance treatment of ALL is not consistently available in developing countries. All these factors contribute to high rates of non-compliance and abandonment in developing countries.

**Interventions to prevent non-compliance and abandonment**

No controlled intervention study has been conducted to improve treatment compliance in pediatric oncology. Intervention studies focused on other aspects such as pain management for invasive procedures, psychosocial education for improving knowledge, and stress management of parents. Studies on interventions to improve compliance for other diseases found that the interventions were complex and labor-intensive including various combination interventions: education, counseling, use of reminders, self-monitoring, reinforcement, family therapy and additional support or attention.

Some studies found that financial and transportation support for families, twinning-programs (collaboration between center in developing countries and more developed countries), and locally adapted protocols are important to reduce treatment refusal and abandonment.

**REPUBLIC OF INDONESIA: EXPERIENCE WITH TREATING CHILDDHOOD ALL**

The Republic of Indonesia is a country of South East Asia and the world's largest archipelagic state, consisting of 5 main and approximately 17,500 smaller islands. The country has a total of around 2.9 million km square with only around 50% land territory. Based on the census of 2000, Indonesia has around 206 millions inhabitants, and was estimated to be almost 220 million in 2003 and this makes Indonesia the world's fourth most populated nation. The proportion of children under 15-year-old was 29%.

The exact prevalence and incidence of ALL in Indonesia is not known. The incidence of ALL is thought to be more or less equal worldwide. A childhood leukemia incidence of 2.5 to 4.0 new cases per 100 000 children leads to an estimated 2000 to 3200 new childhood ALL cases each year in Indonesia.

In Indonesia different ALL treatment protocols have been used during the last decades. Patients were treated with the Comprehensive Protocol ALL of Childhood 1992 (COM-ALL-92) protocol from 1997 until 1999, by the Wijaya Kusuma-ALL-99 pilot protocol from 1999 till 2000, by the Wijaya Kusuma-ALL-2000 protocol until December 2005, and starting December 2005 the Indonesia-ALL-2006 protocol is recently used. According to the protocols, patients are stratified into standard risk (SR) or 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/mm 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. These protocols consist of various phases: 7 weeks induction, 6 weeks consolidation, and 2 years maintenance. HR patients have a more intensive and extensive protocol: more drugs (daunorubicin, L Asparaginase are added in induction phase) and re-induction phase is added after consolidation phase.

Our study found that the overall event-free survival was only 20%. The
cause of treatment failure was mainly due to treatment refusal or abandonment (35%), secondly was treatment-related death (23%), and progressive or relapsed leukemia (22%). The main problem in treating ALL is due to poverty and low educational status. It is estimated that 18% of the Indonesian population lives below the poverty line and 49% lives on less than US$2 per day. The poor parents are not able to pay for the medical care, particularly the expensive prolonged care and costly drugs required for pediatric leukemia.

Even though, the government provides nine years of basic education, six years of primary school and three years of junior high school, in 2002, the literacy of Indonesian people was 87.9% (more men than women: 92.5% versus 83.4%), 31.8 million people had attended primary school and 18.6 million secondary school. Lack of education and little awareness of health-issues delay the seeking of medical help. Consequently, the children often come later with a more advanced stage of leukemia. Due to lack of knowledge regarding health problems, especially rare problems as childhood leukemia, parents do not understand why extended therapy is necessary as soon as their child appears to be healthy again.

Pediatric oncology centers are limited, making their access difficult or impossible for less affluent parents as they cannot even afford the transportation costs to reach the distant clinic. The numbers of qualified physicians and nurses are far too little for the excessive amount of patients. Childhood ALL is usually treated in third level referral-teaching hospitals. Most patients have no consistent pediatric oncologist and they are treated by monthly rotating residents who have no appropriate knowledge and skill for treating childhood ALL. High prevalence of malnutrition and infectious diseases make children with leukemia more vulnerable and less tolerant of chemotherapy. On the other hand, facilities for supportive care are often inadequate. The chemotherapeutic drugs and antibiotics are in short supply or not available at all. All these factors increase treatment failure in Indonesia.

To decrease abandonment rate, a program was instituted in January 2004 at Dr. Sardjito Hospital, Yogyakarta, where our studies were conducted. It consists of a structured parental education-program (PEP), donation of chemotherapy for all new ALL patients and a randomized intervention by providing a diary book for assigned ALL patients. The parental education program consisted of education about leukemia, its treatment, availability of donated chemotherapy, informed-consent, statement of understanding for donated chemotherapy and a complaints-procedure. A multi-methods approach: verbal explanations, information-booklet, audiocassette, and DVD was used to present the PEP.

AIMS OF THE THESIS

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 of a medication-diary-book in the 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 outcome of childhood ALL? (chapter 7 and 8).

OUTLINE OF THE THESIS

Chapter 1 General introduction. In this chapter relevant scientific literature is reviewed.
Chapter 2 Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: an analysis of causes and consequences. This chapter describes an exploratory descriptive study by interviewing families of ALL patients who refused or abandoned treatment. It will analyse reasons and consequences of treatment refusal or abandonment.
Chapter 3 Chemotherapy-related side-effects in childhood ALL in Indonesia: Parental perceptions. In this chapter the frequency and severity of side-effects in childhood ALL and its impact on treatment compliance and daily activities are analyzed.
Chapter 4 Health-related quality of life assessment in Indonesian childhood acute lymphoblastic leukemia. In this chapter the health-related quality of life in Indonesian childhood ALL patients and the influence of
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demographic and medical characteristics on HRQOL is assessed.

Chapter 5
Health-care providers’ compliance with childhood acute lymphoblastic leukemia protocol in Indonesia. In this chapter, knowledge and attitude of health-care providers toward protocol compliance is described.

Chapter 6
Attitude of health-care providers toward childhood leukemia patients with different socio-economic backgrounds. This chapter describes how parental socio-economic status influences beliefs, attitude, and behavior of health-care providers treating childhood leukemia.

Chapter 7
A medication diary-book for parents of childhood acute lymphoblastic leukemia in Indonesia: treatment outcome from a randomized trial. In this chapter the effect of using a diary-book on treatment outcome of childhood acute lymphoblastic leukemia will be presented.

Chapter 8
A medication diary-book for parents: a compliance tool for acute lymphoblastic leukemia treatment? In this chapter evaluation of using a diary-book and its related factors will be discussed.

Chapter 9
General discussion reviewing all data and presenting suggestions for future research.

Chapter 10
Summary and conclusions

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