CHAPTER 9

General discussion

In Indonesia, until recently there were no published data on the epidemiology and treatment outcome of childhood acute lympoblastic leukemia (ALL). This might be because the cancer registries of the pediatric cancer units (PCUs) in Indonesia were not yet well organized and/or because the national cancer registry in Indonesia had not yet been established.

In 1998 the PCU of Dr. Sardjito Hospital (DSH, Yogyakarta, Indonesia) developed a computerized hospital-based cancer registry for research purposes in line with the development of the Indonesian WK-ALL-1999 pilot protocol for childhood ALL.[1] The data were organized by a data manager and stored as hard copy in a data folder and also digitally stored using an Excel file and the Statistical Package for the Social Sciences (SPSS) file format. The data used in the studies presented here are derived from that registry.

The main focus of the studies in this thesis is on childhood ALL patients treated in the PCU of DSH . The research covers the epidemiology of acute leukemia, measurement of treatment response, and clinical trials to improve treatment outcome of these young patients. The investigations and results will be used to achieve our aim to develop the best possible treatment strategies for childhood ALL in Indonesia in the future.

Incidence of childhood acute leukemia in Dr. Sardjito Hospital

In most low-income countries, due to the lack of population-based and hospital-based cancer registries, data related to the epidemiology of childhood cancer are either very scarce or are not reliable. In those countries, including Indonesia, the main obstacles to developing a well-organized registry are limited resources and lack of funding. Our epidemiology study presented in **Chapter 2** revealed that the annual incidence rate of childhood ALL in Yogyakarta Special Province has been increasing over the last 10 years, and that the estimated average annual incidence rate of childhood ALL is lower compared with that in Western countries.[2]

A wide variety of factors have contributed to the apparently increasing incidence of childhood acute leukemia in our PCU: these include an improvement in diagnostic capacity, an increasing number of referrals, an increase in the general public's knowledge and awareness of cancer, improvement in the government program for better/easier

access to medical services, and well-organized cancer registries. Improving the network between our PCU and that of the surrounding hospitals has also contributed to the higher referral rates from a wider area.

A slight increase in the incidence of acute leukemia has also been reported in Western countries;[3-5] their data are based on well-established cancer registries and governmental health systems for cancer treatment. There are at least two hypotheses related to the incidence of childhood leukemia in the Western setting concerning the immune system: these include the delayed-infection hypothesis[6] and the population-mixing hypothesis.[7] These hypotheses suggest that early infectious insulation may predispose an aberrant response of the immune system in susceptible individuals after delayed exposure to infections at an age commensurate with increased lymphoid cell proliferation. However, it remains unclear whether both these hypotheses are also valid when applied to Indonesia - a geographical setting in which infection is a major problem in the community. Although every Indonesian child is exposed to infections from an early age, the incidence of acute leukemia in these children continues to increase. The increasing number of children with leukemia will lead to an increasing burden on their families and the government, since 73% of the patients in our PCU are from poor families[8] and are dependent on the governmental health insurance intended for the poor, the so-called *Jamkesmas (Jaminan Kesehatan Masyarakat)* program. Moreover, due to the existence of various bureaucratic obstacles, not all patients from poor families are able to access this type of community health insurance. Even those who are covered by the *Jamkesmas* program or by some other type of insurance, still have to pay for transportation and the many other daily expenses during hospitalization; these costs are generally beyond the means for most poor families. Moreover, we have seen that many parents lose their job because they had to accompany their child who was hospitalized in our PCU for a relatively long period of time.[9]

Variation in the incidence of childhood ALL is well documented in international reports.[10] In our study, the relatively low average annual incidence rate of childhood ALL (20.8/million person years) compared with that in Western countries (22.4 - 37.9/million person years) must be viewed with caution because of the inaccuracy of our population data and/or of the catchment area used to calculate the incidence. In addition, the highly acute and fatal characteristics of ALL may imply that some children die before they have been properly diagnosed and categorized.

This possibility is emphasized in Indonesia by the high mortality rate of children aged under 5 years. Howard et al.[11] reported that the incidence rate of childhood leukemia is systematically underestimated in the setting of (very) low-income countries. Various obstacles related to infrastructure and to social and economic issues (all typically seen in low-income countries) may be faced when quantifying the incidence of cancer.[12] For example, parents may not be aware of the early signs of cancer, or do not have access to a medical facility. When they do arrive at a hospital, that facility may lack the resources and/or the medical equipment to enable accurate diagnosis and treatment. Moreover, when the diagnosis has been confirmed, the family may have insufficient resources to pay for adequate treatment in a hospital. In that case they may turn to alternative (less costly) treatments or seek traditional healers in the belief that they can help. This may eventually lead to refusal of treatment before the patient has been properly registered, or abandonment after treatment has started. All of these limitations may not necessarily play a large role in Yogyakarta Special Province, since primary health care is well organized and it appears that the majority of children with leukemia do reach the PCU. In our study, of all acute leukemia cases, the relatively low incidence of ALL may explain the relatively high percentage of acute myeloid leukemia (AML) cases compared to Western countries. The incidence of AML that we found in Yogyakarta Special Province is very similar to that reported in Western countries.

Proper diagnosis also plays a pivotal role in the rising incidence rate of childhood leukemia. To improve the diagnosis of childhood leukemia, the World Health Organization recommends the use of immunophenotyping, besides morphologic examination. The immunophenotype examination was introduced in our PCU in 2006. The study presented in **Chapter 3** revealed that the immunophenotypic pattern of childhood ALL in Indonesia was similar to that found in Western countries, with precursor B-cell ALL in 80 - 85% of patients.[13] Identification of the lineage is important for treatment management, since the treatment approach and outcome of both lineages differs in relation to the biological characteristics and the prognostic factors.[14-18] T-lineage ALL is frequently associated with male gender, an older age group (10 years or more), hyperleukocytosis, and the existence of a mediastinal mass. Historically, the prognosis of T-lineage ALL patients was worse than that of precursor B-cell ALL patients; however, with the more intensive treatment in Western countries the outcome of patients with T-lineage

ALL has improved, as has the outcome of those with precursor B-cell ALL.[17,19,20]

It is beyond doubt that the immunophenotype examination has improved our risk group stratification, previously based on the consensus criteria of the Rome/National Cancer InstituteWorkshop[21]and the day-8 response to dexamethasone treatment (Chapter 5). After the introduction of the immunophenotype examination, in our PCU all T-lineage ALL patients are classified and treated as high-risk patients since we do not have a separate protocol for T-lineage ALL, as is the case in some Western studies. However, further studies are needed to confirm whether the improved treatment outcomes of the Indonesia-ALL-2006 protocol compared to the WK-ALL-2000 protocol is due (in part) to better risk classification using immunophenotype in the Indonesia-ALL-2006 protocol. Immunophenotyping is also important to distinguish between ALL and AML. Despite the good level of concordance between immunophenotype examination and morphological assessment in our PCU (kappa=0.82), 6.6% of our patients still shifted from ALL to AML protocols (or vice versa) based on immunophenotypic data.

The immunophenotype examination is feasible in Indonesia and has been validated by the Hematology Laboratory of the VU University Medical Center, Amsterdam (the Netherlands). It is useful for epidemiological studies and for guiding clinical treatment. Therefore, priority should be given to establishing immunophenotyping in all PCUs in Indonesia, or bone marrow should be sent to the referral hospitals for analysis. Once again, an ongoing problem is the lack of financial resources. During our research project the costs of immunophenotype analyses were covered; however, this item is not yet reimbursed by Indonesian health insurance companies and most families cannot afford to pay these high costs.

Evaluation of early treatment response and its role as predictor for outcome

A correlation has been shown between early response to treatment and the prognosis of childhood ALL.[22-28] Early response can be monitored by morphology of blood and/or bone marrow in the first few weeks of induction treatment. Nowadays, however, in Western countries sophisticated methods are applied to assess minimal residual disease: very low numbers of leukemic cells remaining in bone marrow. However,

in Indonesia it is not yet possible to study minimal residual disease using flow cytometry and polymerase chain reaction. Our morphological study on identifying apoptotic cells in peripheral blood by light microscopy **(Chapter 4)** showed that cells undergoing apoptosis could be detected in peripheral blood during the second week after start of treatment. This method has also been successfully applied by others.[29-32] However, the precise time point at which to conduct this measurement is not yet established and the cut-off point to determine the classification of the patient has not yet been determined. Thus, although this method is simple, cheap and highly reproducible it is not yet ready for daily application.

The least traumatic and easiest method to assess early response to treatment is to measure the remaining leukemic cells in blood using a routine complete blood count test. In this way patients can be stratified based on the absolute number of lymphoblasts in the circulation after 7 days of treatment with oral dexamethasone plus one dose of intrathecal methothrexate: good responders are defined as those with less than 1000/µl and poor responders as those with 1000/µl or more. Our study in **Chapter 5** showed that the percentage of our patients with poor response was higher (19.4%) than that reported in most Western countries (7.5 - 15%) in patients treated with prednisone or prednisolone.[33,34] However, our patients often received delayed administration of intrathecal methotrexate from the schedule at day 1 of entering treatment. Thyss et al.[35] clearly showed that postponing intrathecal methotrexate injection generated an increasing percentage of poor responders. In our setting, the poor responder patients are significantly associated with adverse presentation at diagnosis (age 1 year or 10 years or more, WBC count 50,000/µl or more) and more-resistant disease, compared to patients classified as good responders. These results are in line with those reported for studies in Western countries.[36] Remarkably, our study failed to show that poor responder patients have a significantly higher relapse rate than that reported in Western studies.[36] This might be because, in our study, fewer patients are expected to develop a relapse since many absconded or died before a relapse could occur. We implement the day-8 response measurement as a criterion in risk stratification for the Indonesian protocols, where standard-risk patients with poor response will be shifted over and treated as high-risk patients. In comparison with treatment-response evaluation using bone marrow samples,[37] this method is cheaper and less invasive. However, for this type of risk classification to succeed, this criterion must be consistently applied by physicians and nurses in all our PCUs.[38]

Adverse events and clinical trials in the Indonesian treatment protocols

The many factors that determine the success of treatment in childhood ALL include the treatment protocol, compliance with treatment, response to treatment in clearing the lymphoblasts from the body, access to supportive care, and the experience and knowledge of the PCU team. The adverse events that we consider to be treatment failure are treatment refusal, abandonment, toxic death, and resistant disease or relapse. The frequency of the occurrence of these events differs between Western and low-income countries.

By definition, refusal of treatment occurs before entering treatment while abandonment of treatment occurs during treatment. Both events are a major cause of death in children suffering from ALL, both often occur in low-income countries and can affect 16 - 50% of the cases.[39] Studies in our PCU and other low-income countries showed that abandonment was related to multiple factors including financial issues, problems with transportation to hospital, lack of access to medication from the hospital, etc. Besides these practical issues, personal factors also play a role such as the belief that childhood ALL is not curable, experiencing a traumatic procedure at diagnosis and/or during treatment, being confronted with undesired side-effects, lack of adequate or satisfactory communication with healthcare providers in the PCU, etc.[39-43] In our PCU, behavioral alteration in a child was the most frequent and bothersome side-effect reported by 92% of the parents. Some children may become stubborn and disobedient, or are so frightened of the medical procedures that this leads to abandonment of treatment.

Of all our patients who abandoned treatment, the majority (25/57 or 44%) did so during the induction phase at the start of implementation of the Indonesian protocol in 1997 - 2002.[8] This illustrates that during induction treatment patients and families are in a highly critical situation and are faced with catastrophic problems. They are often in denial of the diagnosis and treatment, have difficulty entering the intimidating hospital environment, and are confronted with the toxic side-effects of treatment. The family income may decrease due to time lost from work, or debts may accrue to cover the rising costs of hospitalization.[43] Currently, efforts are being made to prevent treatment abandonment and to improve the outcome of these children. A diary for parents has been devised in which they can write down the medication taken according to the

treatment schedule, the laboratory results, and other specific events during the course of treatment. Also, some progress has been made since theintroduction of a structured parental education program[44] and thanks to increased donations of medicines from charitable institutions in Indonesia and the Netherlands.[45] However, despite all these efforts, in our PCU the incidence of treatment abandonment has not decreased: in the period 2000-2005 it was 37/165 (22.4%) and in the period 2006 - 20011 it was 49/196 (25.0%). We should mention that the number of patients abandoning treatment might even become higher in the latter period because not all patients have completed their 2-year treatment schedule (Table 1). We anticipate that treatment abandonment will become an even greater problem in our geographical setting. The rate has not diminished in the last 10 years, and may increase further when the government stops the *Jamkesmas* program, since most of the patients in our PCU depend on it. Mostert et al.[8] showed that three of four patients in our PCU came from poor families and treatment refusal/abandonment occurred in 47% of them compared to only 2% in children from prosperous families. We recently estimated that of all the patients cared for in the 'economy class' of our PCU, 80% are supported by the *Jamkesmas* program, 10% are covered by governmental or a company's health insurance, and the remaining 10% have to pay all the hospital costs from their own pocket. Based on these data, in Yogyakarta we have established a charity committee for children with cancer and are encouraging the Parents' Association to raise funds to sustain our programs. In addition, it is hoped that social programs (e.g. weekly entertainment, play/schooling activities in the hospital organized by NGO family support groups), together with providing a better PCU infrastructure/environment and more treatment rooms will reduce the queues and waiting lists. Altogether, it is hoped that these activities will strengthen our program against treatment abandonment.

Toxic death, mainly caused by infection and hemorrhage, is a major problem in childhood ALL treatment, especially in low-income countries. A study in our PCU conducted in the period 1997 - 2002 showed that toxic deaths (23%) were the second major cause of treatment failure after treatment refusal or abandonment (35%).[8] In **Chapter 6** our double-blind randomized clinical trial using ciprofloxacin versus placebo aimed to reduce the induction death rate caused by infection. Unexpectedly, the findings showed that oral ciprofloxacin offered no benefits for that purpose. We suggest that the lower nadir value of the neutrophil count

found in the ciprofloxacin group compared to the placebo group predisposed for higher mortality in the ciprofloxacin group. This is related to immune depression caused by the leukemia and/or intensive chemotherapy; therefore, lethal infection during neutropenia occurred most often during the induction phase.[46-48] Due to the lack of microbiological assays, the appearance of resistant bacteria could not be confirmed in our study. However, since many studies have reported the emergence of resistant bacteria to ciprofloxacin after its administration for prophylactic purposes,[49-52] for the moment we advise to stop using ciprofloxacin as prophylaxis against infection or sepsis during induction treatment in our PCU. We have limited the use of this drug to a second-line antibiotic in febrile neutropenic patients when the first-line drugs are either not available or show no response. This policy will hopefully reduce the burden of cost and reduce the risk of the emergence of resistant bacteria.

By definition, resistant disease is a failure to achieve complete remission at the end of induction treatment (with more than 5% lymphoblasts in bone marrow), while relapse is the re-appearance or infiltration of lymphoblasts in body organs after having achieved remission. In our studies, resistant disease together with relapse represent the leukemic events. Resistant disease is observed in less than 5% of patients in Western studies, whereas 5.6% of patients treated with the Indonesian protocol were resistant (Table 1). Our early response to treatment study (Chapter 5) showed that poor responder patients were associated with resistant disease, similar to the findings in Western studies.[36,37]

Relapse is the most common cause of treatment failure in Western countries. For example, a Dutch study reported that relapse affected 15.8% of their patients.[53] Although patients with relapse may achieve a second or third remission thereafter, the outcome remains poor. Second event-free survival after bone marrow relapse is reported to range from 5 - 57%, depending on the duration of the first remission.[54,55] In addition, relapse will also be a burden which increases the costs and toxicity of chemotherapy. In our setting, relapse as the first event after remission was suffered by 38.5% of patients treated on the WK-ALL-2000 protocol and by 11.3% of patients treated on the Indonesia-ALL-2006 protocol; however, because the follow-up period of these two protocols is very different the relapse rates are not totally comparable. The follow-up time of the Indonesia-ALL-2006 is still short with a median time for patients

in remission of 1.9 years (range: 3 months - 5.7 years) whereas the follow-up time for the WK-ALL-2000 protocol is now over 8.2 years for all patients (Table 1). Relapse will probably be our next major problem when treatment abandonment and toxic death rate have been significantly reduced, or after long-term follow-up with a greater number of patients. Central nervous system (CNS) leukemia, initial or as relapses, constitute a special problem in many low-income countries, also in our PCU. First of all, the diagnosis is not always easy. In the past, traumatic lumbar punctures often occurred due to the inexperience of physicians, which impaired the diagnosis of CNS involvement. In such cases, in our setting undertreatment may have led to the occurrence of CNS relapses. Although CNS leukemia is treated with intrathecal medication, systemic therapy is also important. Studies aimed at preventing relapse in the USA and Europe showed that *E coli*-derived L-asparaginase was superior to Erwinase-derived L-asparaginase[19,56] and that dexamethasone was more effective than prednisone.[57-59] Both of these options were studied in this thesis. Because L-asparaginase is the most costly drug in this protocol, we decided to study the dosage of this drug. Our randomized study showed no benefit of three additional doses of L-asparaginase during consolidation in the WK-ALL-2000 protocol **(Chapter 7)**. We found no significant differences in relapse rate and sites of relapse between the group of patients who did receive and those who did not receive treatment intensification using L-asparaginase. Also, in both groups there was no difference in either disease-free survival or event-free survival.

Another randomized trial, reported in **Chapter 8,** was conducted to study whether the use of prednisone instead of dexamethasone as steroid in the Indonesian protocols would improve outcome. Based on the results of Western studies, in Indonesia dexamethasone was the drug of choice in the ALL protocols since 1992. However, doubts arose because the toxicity profile of dexamethasone was higher than that of prednisone. The results of our randomized study in the Indonesia-ALL-2006 protocol show a trend toward better outcome in the prednisone arm compared with the dexamethasone arm, but the difference is not (yet) significant. This result differs from that in Western studies which reported that dexamethasone generated better event-free survival and lower CNS relapse rates than prednisone. However, since our result is based on a relatively low number of patients and with a relatively short follow-up period, further evaluation on long-term follow-up with a greater number of patients is needed to definitely confirm or refuse our findings.

Treatment outcome of Indonesian WK-ALL-2000 and Indonesia-ALL-2006 protocols

Historically, three consecutive protocols have been implemented in our PCU. The first generation (1992-1999) was adopted from the Dutch ALL-VI study[60] and was named the comprehensive ALL protocol (COM-ALL 1992 protocol). The next protocol was the WK-ALL-1999 introduced during 1999 - 2000 as the pilot protocol and accepted as the national Indonesian protocol WK-ALL-2000. The WK-ALL-2000 protocol was implemented from 1999 through 2005 and was then replaced by the Indonesia-ALL-2006 protocol from 2006 until the present day.

The WK-ALL-2000 was developed in the setting of poor access to supportive care, lack of protocol adherence, and the Asian economic crisis in 1998 that caused severe financial problems for the majority of the Indonesian population. Therefore, we proposed to implement the WK-ALL-2000 protocol as a 'less intensive' regimen to meet the situation at that time. The term 'less intensive' was meant to indicate lower costs of drugs, fewer complications, and less costs of supportive care. After the economic situation improved, the Indonesia-ALL-2006 protocol was designed to be 'more intensive' than the WK-ALL-2000 and an anthracycline agent (daunorubicin or doxorubicin) and more doses of L-asparaginase were introduced in the induction treatment plus an intravenous 'high-dose' methotrexate (1000 mg/m^2) in the consolidation treatment. Both the WK-ALL-2000 and the Indonesia-ALL-2006 protocols use the same risk group stratification, namely standard risk and high risk based on presentation at diagnosis, and treatment response at day 8. Immunophenotyping was performed only in the Indonesia-ALL-2006 protocol in a research setting.

Details on the analysis of the outcome of the WK-ALL-2000 and Indonesia-ALL-2006 protocols are presented in Chapter 5 and Chapter 8 of this thesis. The Indonesia-ALL-2006 has resulted in better overall survival than the WK-ALL-2000 protocol (Table 1). The 3-year event-free survival has shown a significant increase from 27% in the WK-ALL-2000 to 37% in the Indonesia-ALL-2006 protocol (P<0.01) (Figure 1). This achievement can mainly be attributed to the significant decrease in deaths in complete remission and less relapse in the Indonesia-ALL-2006 protocol.

Now that death in remission has decreased significantly, in our PCU setting induction treatment is the critical time period for deaths. Because our clinical trial aimed to reduce toxic death caused

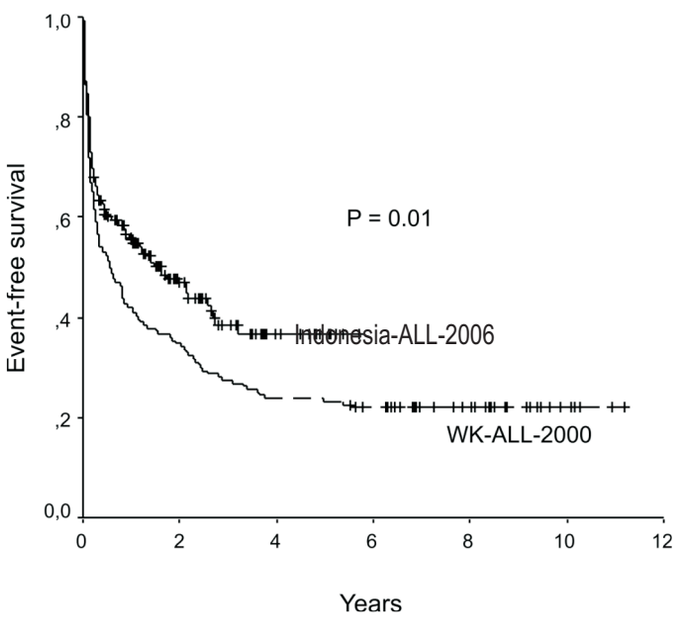

FIGURE 1. **Kaplan-Meier curves of event-free survival of the WK-ALL-2000 protocol (1999 - 2005, n=165) and the Indonesia-ALL-2006 (2006 - 2011, n=196) protocol for standard-risk and high-risk patients.**

by ciprofloxacin prophylaxis during induction (Chapter 6) showed no benefits, additional efforts are required to minimize the induction death rate. The post-induction protocol in the Indonesia-ALL-2006 protocol seems to be better than in the WK-ALL-2000 protocol. The introduction of intravenous cyclophosphamide and a 'high dose' of methotrexate during consolidation for standard-risk and high-risk patients, and cytarabine in the re-induction treatment for high-risk patients, have strengthened the efficacy of the Indonesia-ALL-2006 protocol. On the other hand, the six doses of L-asparaginase during induction in the Indonesia-ALL-2006 protocol may increase toxicity, whilst improved efficacy was not demonstrated.

Separate analysis of the adverse events in the standard-risk patients treated with the Indonesia-ALL-2006 protocol (Chapter 8) shows a trend for a higher induction death rate in the dexamethasone arm than in the prednisone arm (P=0.06). This finding is in line with previous studies showing a tendency towards higher septicemia and induction deaths in childhood ALL treated with dexamethasone than with prednisone or prednisolone.[61-63] On the other hand, the introduction of an anthracycline as the fourth drug in induction will augment the toxicity of dexamethasone.[64]

TABLE 1. **Treatment outcomes during induction treatment, after remission and overall in standard-risk and high-risk patients by protocol.**

	WK-ALL-2000 (n=165)		Indonesia-ALL-2006 (n=196)		Total (n=361)		OR	95%CI	*P*-value
	n	(%)	n	(%)	n	(%)			
Induction outcome									
Complete remission	117	(70.9)	142	(72.4)	259	(71.7)			
Induction failures	48	(29.1)	54	(27.6)	102	(28.3)	0.93[a]	0.59-1.47	0.75
Abandonment	20	(12.1)	23	(11.7)	43	(11.9)	0.95[a]	0.50-1.81	0.87
Death	17	(10.3)	22	(11.3)	39	(10.8)	1.07[a]	0.54-2.10	0.85
Resistant disease	11	(6.7)	9	(4.6)	20	(5.6)	0.67[a]	0.27-1.68	0.39
First event after CR									
Continuous CR	36	(30.7)	90	(63.4)	126	(48.6)			
Abandonment	17	(14.5)	26	(18.3)	43	(16.6)	0.61[b]	0.30-1.26	0.18
Death	19	(16.3)	10	(7.0)	29	(11.2)	0.21[b]	0.09-0.50	<0.01
Relapse	45	(38.5)	16	(11.3)	61	(23.5)	0.14[b]	0.07-0.28	<0.01
Overall outcome									
Continuous remission	36	(21.8)	90	(45.9)	126	(34.9)			
Treatment failures	129	(78.2)	106	(54.1)	235	(65.1)	0.33[c]	0.21-0.52	<0.01
Abandonment	37	(22.4)	49	(25.0)	86	(23.8)	0.53[c]	0.30-0.94	0.03
Death	36	(21.8)	32	(16.3)	68	(18.8)	0.36[c]	0.19-0.66	<0.01
Leukemic events	56	(33.9)	25	(12.8)	81	(22.4)	0.18[c]	0.10-0.33	<0.01
3-year EFS	26.8±3.5%		36.7±4.4%						0.01
Median observation for survivors (range)	8.2 (5.5 -11.2 years)		1.9 (3 months - 5.7 years)						

OR, odds ratio for the Indonesia-ALL-2006 protocol relative to the WK-ALL-2000 protocol; CI, confidence interval; CR, complete remission; EFS, event-free survival. **a,** ORs for any induction failure and specific induction failures (CR during induction is the reference outcome category); **b,** ORs for the first event after achieving CR (continuous CR is the reference outcome category); **c,** ORs for any overall treatment failures and specific treatment failures (continuous CR is the reference outcome category); *P*-value was calculated with the Chi-square test; The WK-ALL-2000 protocol was implemented during 2000-2005 and the Indonesia-ALL-2006 protocol during 2006-2011.

We conclude that the results of the clinical outcome of the Indonesian protocols still lags behind the data reported in American and European studies during 1980-1990, which resulted in complete remission rates of more than 95% and a 5-year event-free survival ranging from 65-83%. Our survival rate in the WK-ALL-2000 protocol during 1999 - 2005 is similar to that of patients treated in the Children's Cancer Group clinical trials conducted in 1970 - 1972. However, the development of Indonesian childhood ALL treatment protocols has shown significant progress in outcomes during the last 10 years. Since the induction phase remains the crucial period for adverse events, efforts are still needed to minimize induction failure and maximize post-induction achievement in the next Indonesian protocol for childhood ALL. Thus, improving the access to adequate supportive care and treatment adherence is much more important than the introduction of a more intensive induction protocol. Eventually, the treatment of childhood ALL in the Indonesian setting will further improve and the chance for cure will increase accordingly. In general, until now, the results of our clinical trials to improve outcome in Indonesian children suffering from ALL do not meet our expectations. We will further optimize our protocols and perform clinical trials with the aim to obtain better results in the future.

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