CHAPTER 8

Dexamethasone versus Prednisone in Childhood Acute Lymphoblastic Leukemia Treatment: Results of the Indonesian Randomized Trial

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Submitted

ABSTRACT

Background. Randomized trials report that, compared to prednisone, dexamethasone has reduced CNS relapse and improved event-free survival (EFS), despite a trend toward a higher risk for induction death. Because toxic death is a specific problem in the Indonesian setting, this study compares the outcome of dexamethasone versus prednisone.

Methods. In the period 2006-2011, 196 patients with childhood acute lymphoblastic leukemia (ALL) treated on the Indonesia-ALL-2006 protocol [first standard risk (SR) and later high risk (HR) patients] were randomized to receive dexamethasone or prednisone as steroid. Patients in the dexamethasone arm (n=102: 68 SR, 34 HR) received dexamethasone 4 mg/m^2/day (SR) or 6 mg/m^2/day (HR), while the prednisone arm (n=94: 66 SR, 28 HR) received prednisone 40 mg/m^2/day (SR and HR).

Results. Patients in the dexamethasone arm showed no significant difference compared to the prednisone arm in abandonment rate (24.5% vs. 25.5%, *P*=0.91), death rate (17.7% vs. 14.9%, *P*=0.54), or leukemic events (13.7% vs. 11.7%, *P*=0.59). After stratification for risk group, a trend towards a higher death rate was found in the dexamethasone arm of SR patients (16.2% vs. 6.1%, *P*=0.06). The 3-year survival for EFS in SR and HR patients for dexamethasone versus prednisone was 31.5 ± 6.6% vs. 41.5 ± 5.9% (*P*=0.51), for leukemia-free survival (LFS) it was 63.7 ± 9.3% vs. 74.5 ± 7.6% (*P*=0.47), and for overall survival (OS) it was 49.5 ± 7.7% vs. 69.3 ± 6.1% (*P*=0.09).

Conclusions. In our setting, a trend toward higher induction deaths was observed in the dexamethasone arm of SR patients. The 3-year EFS, LFS and OS rates were lower in the dexamethasone group; however, these differences were not significant.

Introduction

Steroids, either prednisone or dexamethasone, are essential drugs in the remission induction phase of childhood acute lymphoblastic leukemia (ALL) treatment based on their activity against lymphoblasts.[1-3] In vitro studies and clinical trials showed that dexamethasone is superior to prednisone in killing lymphoblasts,[4,5] and in lowering the incidence of central nervous system (CNS) involvement due to higher concentration of free drug and greater capacity to penetrate the blood-brain barrier than prednisone.[6-8] Randomized trials in Western countries have shown that dexamethasone results in higher event-free survival (EFS) and fewer CNS relapses than prednisolone. However, this might be at the expense of higher toxic deaths even though (due to low numbers) this effect did not reach significance.[8,9] A systematic review and meta-analysis published after our randomization procedure confirmed the findings of significantly lower CNS relapse and reduced events in the dexamethasone group compared with the prednisone group.[10] However, drug-related toxicity was significantly higher with dexamethasone than with prednisone in terms of induction death,[8,11] risk of fractures,[12] gastritis and weight gain.[13] With the much higher toxic death rates (17% - 23%) reported in low-income countries,[14-17] the toxicity of dexamethasone might prove to be excessive.

Since 1992, the Indonesian protocols for childhood ALL were dexamethasone based rather than prednisone based.[16] However, because doubts arose about the toxicity of dexamethasone, we conducted a prospective randomized study to evaluate whether the type of steroid used might influence the outcome in our local setting. The problems frequently encountered in Indonesia and other low-income countries (e.g. treatment abandonment, toxic death, resistant disease and relapse) were evaluated.

Methods

Patients

This prospective study was conducted in the Pediatric Cancer Unit (PCU) of Dr. Sardjito Hospital, Yogyakarta, Indonesia. Childhood ALL patients newly diagnosed during the period from May 22, 2006 (standard risk, SR) or May 1, 2009 (high risk, HR) until December 28, 2011 were

enrolled in this study. The study was started first in SR patients and later expanded to include HR patients. All patients were treated according to the Indonesia-ALL-2006 protocol. Diagnosis of ALL was primarily based on morphological assessment using the French-American-British (FAB) classification and was supported by immunophenotype examination. Patients with FAB-L3 morphology or mature B-ALL were excluded. The inclusion criteria were: age 0 - 14 completed years, newly diagnosed, and no prior treatment with steroids or chemotherapy. Informed consent was signed by parents or guardians. Criteria for SR were age 1 - 10 years, WBC less than 50,000/µl, no mediastinal mass, no CNS involvement, and B-cell lineage as well as a blast count of less than 1000/µl after the 1-week pre-phase treatment. All other patients were classified as HR.

Random allocation into the dexamethasone or prednisone arm was done using a computer program after diagnosis and parental approval. The observation period ended March 23, 2012. The characteristics of the patients are shown in Table 1.

Treatment Protocol

The Indonesia-ALL-2006 protocol was the successor of the first generation of Indonesian national protocols for childhood ALL treatment, namely the WK-ALL-2000 protocol.[18] The WK-ALL-2000 protocol was adapted from the Dutch ALL-VI protocol and was based on 3-drug induction with dexamethasone as the steroid.[19] In the Indonesia-ALL-2006 protocol (Figure 1), the induction consisted of 4 drugs including 4 doses of daunorubicin (30 mg/m^2) for SR and HR patients. In the case that daunorubicin was not available it was replaced by doxorubicin at a dose of 20 mg/m^2. After induction patients received a consolidation and maintenance treatment. A re-induction course was inserted after the consolidation treatment in HR patients. Patients in the dexamethasone arm received prednisone 60 mg/m^2/day during one week pre-phase, then dexamethasone 4 mg/m^2/day during induction, and in blocks during maintenance for SR patients; or dexamethasone 6 mg/m^2/day during one week pre-phase, as well as in induction, re-induction and maintenance treatment blocks for HR patients. Patients in the prednisone arm received prednisone 60 mg/m^2/day during pre-phase, then 40 mg/m^2/day during induction and maintenance treatment blocks (SR patients) or prednisone

40 mg/m^2/day during pre-phase, induction, re-induction and in maintenance treatment blocks (HR patients). At the end of the pre-phase SR patients with a peripheral lymphoblast count of more than 1000/µl were switched to the HR protocol.

TABLE 1. **Characteristics of the patients at diagnosis.**

	Dexa-methasone (n=102)		**Pred-nisone (n=94)**		**Total (n=196)**		***P*-value**
	n	%	n	%	n	%	
Risk group							0.59[b]
Standard risk	68	(67.7)	66	(70.2)	134	(68.4)	
High risk	34	(33.3)	28	(29.8)	62	(31.6)	
Sex							0.55[b]
Boy	51	(50.0)	51	(54.2)	102	(52.0)	
Girl	51	(50.0)	43	(45.8)	94	(48.0)	
Age (years)							0.88[b]
1 - 10	86	(84.3)	80	(85.1)	166	(84.7)	
< 1 and ≥ 10	16	(15.7)	14	(14.9)	30	(15.3)	
WBC (/µl)							0.54[b]
< 50,000	80	(78.4)	77	(81.9)	157	(80.1)	
≥ 50,000	22	(21.6)	17	(18.1)	39	(19.9)	
Immunophenotyping[a]							0.69[c]
T-cell ALL	4	(8.9)	2	(5.6)	6	(7.4)	
Pre-B-cell ALL	41	(91.1)	34	(94.4)	75	(72.6)	

a, This examination was performed in 81 patients. Of the remaining 115 patients, 3 had mature B-cell ALL and 112 had no data on immunophenotype; **b,** Chi-square test; **c,** Fisher's exact test.

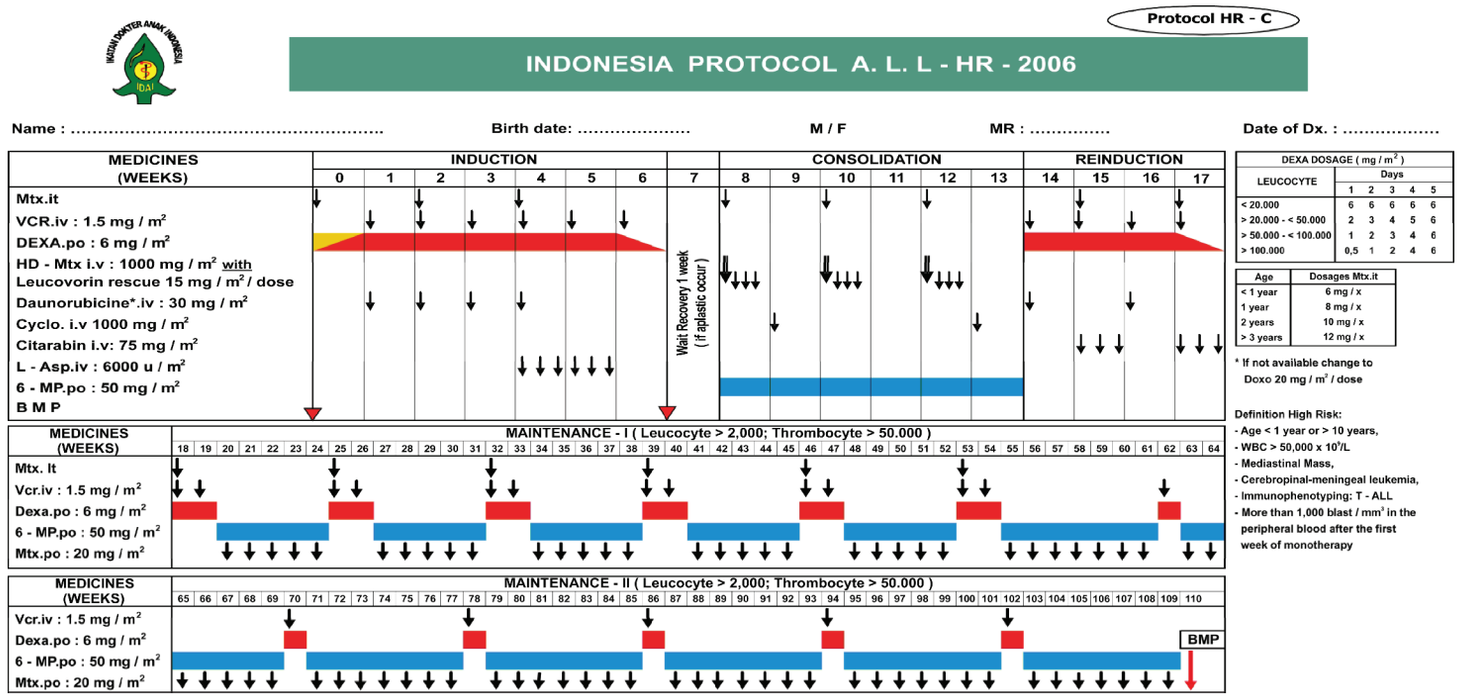

FIGURE 1. **Indonesia-ALL-2006 protocol for high-risk (HR) childhood ALL (dexamethasone arm).** The re-induction treatment was skipped in the standard-risk (SR) patients; otherwise, both the SR and HR protocol have the same drugs and schedules. Patients in the dexamethasone arm received dexamethasone 4mg/m^2/day (SR), or 6 mg/m^2/day (HR). Patients in the prednisone arm received prednisone 60 mg/m^2/day during the pre-phase, then 40 mg/m^2/day during induction, re-induction (HR only), and maintenance treatment blocks.

Outcomes and statistical analysis

The aim of this study was to compare the efficacy of dexamethasone versus prednisone in the Indonesia-ALL-2006 treatment protocol. The outcomes were death rate, abandonment rate and leukemic events (resistant disease and relapse). We calculated EFS from the date at start of treatment to the date of an event which occurred first: death, abandonment, resistant disease or relapse. LFS was calculated from the date at start treatment to the date of resistant disease confirmation at the end of induction, or first relapse after achievement of complete remission (CR). The overall survival (OS) was calculated from the date at start of treatment to the date of death by any cause. CR was determined at the end of induction treatment and defined as no detectable lymphoblasts in peripheral blood or cerebrospinal fluid and less than 5% lymphoblasts in active hemopoietic marrow, and no physical signs of infiltrative leukemic cells anywhere. Patients who were alive without any event were censored at the date of analysis on March 23, 2012. Patients who abandoned treatment whilst in CR, or who relapsed, were considered failures at the time of their withdrawal or relapse. All families of patients were personally contacted on the date of analysis to check the patient's status.

The EFS, LFS and OS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. A *P*-value less than 0.05 was used as level for statistical significance**.** The data were analyzed using the SPSS version 13.0.

Results

During the study period, 291 patients with ALL were admitted to Dr. Sardjito Hospital, Yogyakarta. Of these, 62 did not meet the inclusion criteria due to: refusal of treatment (23), previous treatment with steroids or ALL treatment (9), death before treatment started (8), L3 morphology (8), age at diagnosis 15 years or more (5), mixed leukemia (4), moved to other treatment protocols (4), or to another hospital (1). The remaining 196 patients consisted of 134 SR and 62 HR patients. Immunophenotyping was done in 84 patients and confirmed as T-cell (6) or precursor B-cell ALL (75), while 3 patients were characterized as mature B-cell lineage ALL and thus excluded from this study. For 112 patients no data on immunophenotype were available since the examination was not yet developed at the time of diagnosis, or due to technical problems such as

lack of specimen, clotted specimen or inconclusive results. At the time of analysis all patients had finished induction treatment or experienced induction failure. The median follow-up of patients in remission since entering treatment until the time of analysis was 22 (range: 3 - 60) months in the dexamethasone arm and 26 (range: 4 - 67) months in the prednisone arm (P=0.25). Of the 196 patients enrolled in this study, 102 (52%) were randomized to the dexamethasone arm and 94 (48%) to the prednisone arm. The characteristics at diagnosis such as risk group, age, sex, WBC group and immunophenotype were equally distributed between the dexamethasone arm and prednisone arm (Table 1). The median age was 4.0 years (range: 2 months - 14 years) in the dexamethasone arm and 4.0 years (range: 5 months - 14 years) in the prednisone arm.

Of the 196 patients, 141 (72.4%) patients achieved CR: 71/102 (69.6%) patients in the dexamethasone arm and 71/94 (75.5%) in the prednisone arm (P=0.35) (Table 2). The clinical outcomes in the overall ALL patient group showed no significant differences between the dexamethasone and prednisone arms in terms of abandonment of treatment (24.5% vs. 25.5%, P=0.91), death (17.7% vs. 14.9, P=0.54), leukemic events (13.7% vs. 11.7%, P=0.59) and continuous CR achievement (44.1% vs. 47.9%, P=0.60). In both arms, all relapses were hematological relapses and 76% occurred during treatment, mostly in maintenance treatment (65%). The median time to relapse after achievement of CR was 16 (range: 10 - 30) months in the dexamethasone arm and 22 (range: 2 - 29) months in the prednisone arm (P=0.88). No secondary malignancy was found during this study.

Separate analysis of SR patients revealed a trend for a higher death rate during induction in the dexamethasone compared to the prednisone arm (16.2% vs. 6.1%, P=0.06) with equal abandonment and leukemic events in both arms (Table 3). In HR patients the dexamethasone versus the prednisone arms showed no significant difference in terms of treatment abandonment, death and leukemic events either during induction or overall (Table 4).

The 3-year EFS in the dexamethasone arm was 31.5% ± 6.6% versus 41.5% ± 5.9% (P=0.51) in the prednisone arm (Figure 2). The 3-year LFS in the dexamethasone arm versus the prednisone arm was 63.7 ± 9.3% versus 74.5 ± 7.6% (P=0.47) (Figure 3) and the 3-year OS in the dexamethasone arm versus the prednisone arm was 49.5 ± 7.7% versus 69.3 ± 6.1% (P=0.09) (Figure 4).

TABLE 2. **Clinical outcomes during induction treatment and overall in standard- risk and high-risk patients.**

	Dexa-methasone (n = 102)		Pred-nisone (n = 94)		Total (n = 196)		OR	95% CI	*P*-value
	n	(%)	n	(%)	n	(%)			
Induction treatment									
CR	71	(69.6)	71	(75.5)	142	(72.4)			
Induction failures	31	(30.4)	23	(24.5)	54	(27.6)	0.74	0.39-1.40[a]	0.35[c]
Abandonment	12	(11.7)	11	(11.7)	23	(11.7)	0.92	0.38-2.21[a]	0.85[c]
Death	14	(13.7)	8	(8.5)	22	(11.3)	0.57	0.23-1.45[a]	0.23[c]
Resistant disease	5	(4.9)	4	(4.3)	9	(4.6)	0.80	0.21-3.10[a]	1.00[d]
Overall events									
Continuous CR	45	(44.1)	45	(47.9)	90	(45.9)			
Treatment failures	57	(55.9)	49	(52.1)	106	(54.1)	0.86	0.49-1.51[b]	0.60[c]
Abandonment	25	(24.5)	24	(25.5)	49	(25.0)	0.96	0.48-1.93[b]	0.91[c]
Death	18	(17.7)	14	(14.9)	32	(16.3)	0.78	0.34-1.75[b]	0.54[c]
Leukemic event	14	(13.7)	11	(11.7)	25	(12.8)	0.79	0.32-1.92[b]	0.59[c]

OR, odds ratio for prednisone arm relative to dexamethasone arm; CI, confidence interval; CR, complete remission. **a,** ORs for any induction failure and specific induction failures (CR during induction is taken as the reference outcome category); **b,** ORs for any treatment failures and specific treatment failures (continuous CR is taken as the reference outcome category); **c,** Chi-square test; **d,** Fisher's exact test

TABLE 3. **Clinical outcomes during induction treatment and overall in standard-risk patients.**

	Dexamethasone 4mg/m² (n = 68)		Prednisone 40 mg/m² (n = 66)		Total (n = 134)		OR	95% CI	*P*-value
	n	(%)	n	(%)	n	(%)			
Induction treatment									
CR	48	(70.6)	52	(78.8)	100	(74.6)			
Induction failures	20	(29.4)	14	(21.2)	34	(25.4)	0.65	0.29-1.42[a]	0.27[c]
Abandonment	8	(11.7)	7	(10.6)	15	(11.2)	0.81	0.27-2.39[a]	0.70[c]
Death	11	(16.2)	4	(6.1)	15	(11.2)	0.34	0.10-1.13[a]	0.06[c]
Resistant disease	1	(1.5)	3	(4.5)	4	(3.0)	2.77	0.28-27.54[a]	0.62[d]
Overall events									
Continuous CR	31	(45.6)	35	(53.1)	66	(49.3)			
Treatment failures	37	(54.4)	31	(46.9)	68	(50.7)	0.74	0.38-1.46[b]	0.39[c]
Abandonment	16	(23.5)	13	(19.7)	29	(21.6)	0.72	0.30-1.73[b]	0.46[c]
Death	13	(19.2)	9	(13.6)	22	(16.4)	0.61	0.23-1.63[b]	0.32[c]
Leukemic event	8	(11.7)	9	(13.6)	17	(12.7)	0.99	0.34-2.90[b]	0.99[c]

OR, odds ratio for prednisone arm relative to dexamethasone arm; CI, confidence interval; CR, complete remission. **a,** ORs for any induction failure and specific induction failures (CR during induction is taken as the reference outcome category); **b,** ORs for any treatment failures and specific treatment failures (continuous CR is taken as the reference outcome category); **c,** Chi-square test; **d,** Fisher's exact test

TABLE 4. **Clinical outcomes during induction treatment and overall in high-risk patients.**

	Dexa-methasone 6 mg/m² (n = 34)		Pred-nisone 40 mg/m² (n = 28)		Total (n = 62)		OR	95% CI	*P*-value
	n	(%)	n	(%)	n	(%)			
Induction treatment									
CR	23	(67.6)	19	(67.9)	42	(67.7)			
Induction failures	11	(32.4)	9	(32.3)	20	(32.3)	0.99	0.34-2.89[a]	0.99[d]
Abandonment	4	(11.8)	4	(14.3)	8	(12.9)	1.21	0.27-5.50[a]	1.00[d]
Death	3	(8.8)	4	(14.3)	7	(11.3)	1.61	0.32-8.12[a]	0.69[d]
Resistant disease	4	(11.8)	1	(3.7)	5	(8.1)	0.30	0.03-2.94[a]	0.38[d]
Overall events									
Continuous CR	14	(41.2)	11	(39.3)	25	(40.3)			
Treatment failures	20	(58.8)	17	(60.7)	37	(59.7)	1.08	0.39-3.00[b]	0.88[c]
Abandonment	9	(26.5)	10	(35.7	19	(30.6)	1.41	0.43-4.68[b]	0.57[c]
Death	5	(14.7)	5	(17.8)	10	(16.2)	1.27	0.29-5.55[b]	1.00[d]
Leukemic event	6	(17.6)	2	(7.2)	8	(12.9)	0.42	0.07-2.53[b]	0.43[d]

OR, odds ratio for prednisone arm relative to dexamethasone arm; CI, confidence interval; CR, complete remission. **a,** ORs for any induction failure and specific induction failures (CR during induction is taken as the reference outcome category); **b,** ORs for any treatment failures and specific treatment failures (continuous CR is taken as the reference outcome category); **c,** Chi-square test; **d,** Fisher's exact test

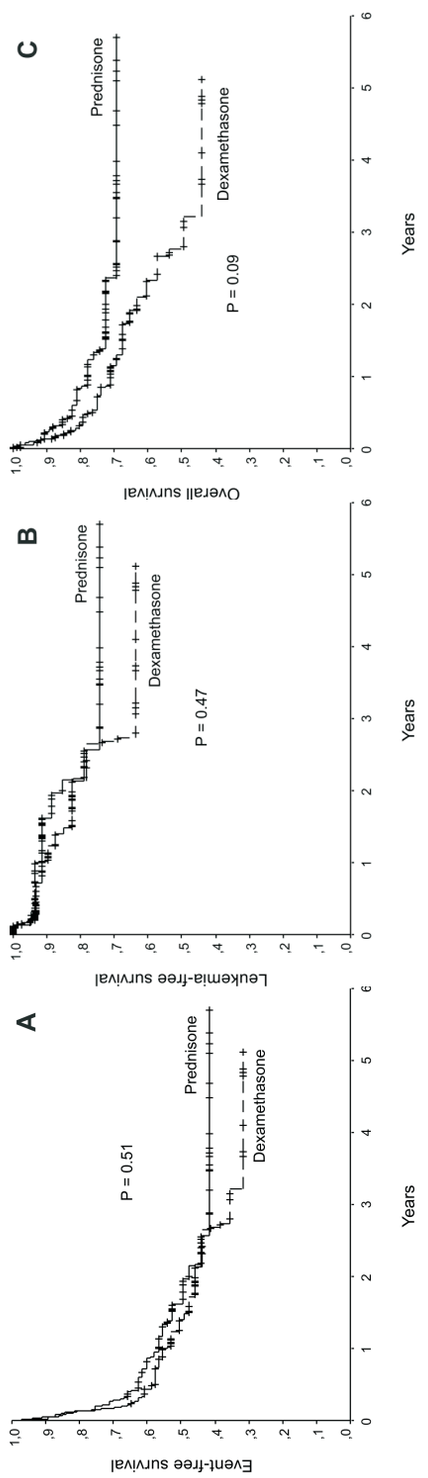

FIGURE 2. **Kaplan-Meier survival curves of the entire group (standard and high-risk together) of childhood ALL patients treated according to the Indonesia-ALL-2006 protocol.** Event-free survival **(A)**, leukemia-free survival **(B)**, overall survival **(C)**.

Discussion

This study compared the efficacy of dexamethasone versus prednisone in newly diagnosed childhood ALL patients treated in a low-income setting in Indonesia. The Indonesian protocols have utilized dexamethasone as steroid for more than 15 years based on the evidence of a lower incidence of meningeal leukemia in childhood ALL patients treated with dexamethasone instead of prednisone[7] and the high cure rate achieved with the dexamethasone-based Dutch ALL-VI protocol.[19] However, a UK randomized study showed that dexamethasone was also associated with more toxicities than prednisone, i.e. treatment-related death in the dexamethasone group was higher than in the prednisone group (4.6% vs. 2.4%, *P*=ns).[8] Considering that toxic death is much higher in Indonesia and other low-income countries compared with Western countries, the question arose whether dexamethasone might be too toxic in the Indonesian setting. The present study was conducted to address this question.

However, the outcomes in the overall ALL cohort showed no significant differences between the dexamethasone and the prednisone arms, including rates of treatment abandonment, death and leukemic events. In our setting, refusal or abandonment of treatment and toxic death during induction treatment or in remission were the major causes of treatment failure. These adverse events occurred in appreciably higher rates than in Western countries where abandonment is almost non-existent and the death rate is reported to be 1 - 5%.[20-24] The high level of treatment refusal and abandonment, and toxic death rates, may represent problems typically seen in low or medium-income countries[14-18,25,26] that lead to inferior survival rates compared to Western studies. Studies in our PCU showed that abandonment of treatment is due to multi-factorial causes related to financial issues (i.e. occurring more often among poorer patients), difficulty with transportation to the hospital, experienced traumatic side-effects, socio-economic status, family perception of disease curability, and lack of professionalism of the health provider (including their attitude/communication skills in ensuring compliance with treatment of patients and parents).[16,27-31] Compared with children enrolled at the implementation of the Indonesian childhood ALL protocol during 1997 - 2002,[16] the ALL children in the present study (2006 - 2011) showed a slight reduction in treatment refusal rate (11% or 18/164 vs. 8% or 23/291, *P*=0.27) and abandonment rate (27% or 39/143 vs. 25% or 49/196, *P*=0.64);

however, both events remain prominent in our daily practice. Many programs have been developed to overcome this problem, including the introduction of a structured parental education program, improvement of access to medicine donation,[32] development of human resources and PCU infrastructure, together with the issuing of a government health insurance program intended for poor people during the last 8 years.[33]

Compared with the previous study in our PCU,[16] the toxic death rate has reduced from 23% (38/164) to 16% (32/196); however, the follow-up procedure between the former protocol and the current protocol differs considerably. The finding that the toxic death rate mostly occurred during induction treatment suggests the important role of supportive care for the life-threatening conditions during this phase. Our study on patients treated with the less intensive Indonesian WK-ALL-2000 protocol (1999 - 2005) in our PCU had resulted in severe neutropenia during induction treatment with a median nadir of absolute neutrophil count (ANC) of 165 (range: 5 - 25,480) cells/µl (data in press). It is generally assumed that lack of access to supportive care is the cause of the high toxic death rates in low-income countries. Separate analysis in the SR patients revealed that the dexamethasone arm tended to have a higher induction death rate (16.2%) than patients in the prednisone arm (6.1%; *P*=0.06). This result is in line with the UKMRC ALL97 study which also found a higher early death (less than 60 days) rate in the dexamethasone group than in the prednisolone group (1.8% vs. 0.7%, *P*=0.07); however, in that study the absolute number was too low to achieve significance.[8] A possible explanation for this could be a notable tendency towards higher septicemia and induction death in childhood ALL treated with dexamethasone than with prednisone or prednisolone.[10,11,23,34] The administration of an anthracycline during induction will augment the toxicity of dexamethasone, as demonstrated by Belgaumi et al.[13] In the UKALL VIII Study those who received daunorubicin during induction experienced twice as many induction failures (non-remitters + deaths) compared with those who did not receive it (6% vs. 3%). Early remission death rates were also higher in those who received daunorubicin (8% vs. 4% of remitters).[35] Based on consensus emerging from the Indonesian Pediatric Hematology and Oncology working group meeting in 2005, the Indonesia-ALL-2006 protocol introduced anthracycline (4 doses of daunorubicin 30 mg/m^2 or doxorubicin 20 mg/m^2) as the fourth drug during induction in both SR and HR patients. In retrospect this decision

may have resulted in more pronounced life-threatening conditions and a higher death rate in the SR group. This is especially relevant in a setting such as Indonesia with its high incidence rate of infections and limited access to supportive care. Studies in Italy, USA and the UK showed that SR patients treated with a 3-drug induction without anthracycline achieved CR rates of about 95% with a 5-year overall EFS of 56% - 83%.[9,35,36] The Dutch protocol ALL-6 and ALL-9, both dexamethasone-based protocols with 3-drug induction for non-HR patients, have generated an overall 5-year EFS of 82% and 84%, respectively.[37,38] This outcome might be related to the better supportive care in Western countries, but perhaps also to the less toxicity in the 3-drug induction protocol thus less induction deaths. In the present study, further analysis in the HR group showed no significantly different outcomes between patients in the dexamethasone and the prednisone arms.

As reported by studies in Western countries, dexamethasone is superior to prednisone in preventing relapse, particularly in the CNS.[7-9] This finding could not be confirmed in our study since all relapses in both arms were hematological ones. In our PCU, lack of experience in diagnosis of CNS relapse may have obscured the finding of CNS relapses. In addition, a short follow-up period may explain why most relapse occurred during maintenance treatment. In terms of protocol efficacy, in the present study the EFS, LFS, and OS showed no significant difference between the dexamethasone and the prednisone arms. However, the prednisone arm showed a trend to have a higher probability of OS at 4 years (69.3 ± 6.1% vs. 44.0 ± 8.6%, P=0.09) than the dexamethasone arm. The non-superior outcome of dexamethasone arm could be partly explained by the administration of a less effective dose of dexamethasone in SR patients. The CCG-1922 study using prednisone 40 mg/m^2 vs. dexamethasone 6 mg/m^2 during induction showed significantly better EFS in the dexamethasone arm.[39] A meta-analysis of 8 Western studies[10] showed a significant reduction of event rate (death from any cause, refractory or relapsed leukemia, or second malignancy) in the dexamethasone arm than in the prednisone arm at a ratio of prednisone and dexamethasone of less than 7. The event rate was the same in prednisone and dexamethasone when the ratio was 7 or more. In terms of preventing relapse, dexamethasone significantly reduced CNS relapse compared with prednisone; this applied to a ratio of prednisone and dexamethasone of both less than 7 and 7 or more. The meta-analysis concludes that dexamethasone is more efficacious than prednisone

in induction treatment for childhood ALL. However, dexamethasone is also more toxic. The Indonesian childhood ALL protocol for HR used 40 mg/m^2 for prednisone and 6 mg/m^2 for dexamethasone, whereas the SR group used the lower dose of dexamethasone (40 mg/m^2 for prednisone and 4 mg/m^2 for dexamethasone). Nevertheless, the induction deaths in the SR dexamethasone group (16.2%) were almost three-fold higher than in the prednisone arm (6.1%; *P*=0.06) (Table 2). Although there is no consensus on dose conversion between dexamethasone and prednisone, the typical conversion between prednisone and dexamethasone is 1 mg dexamethasone equivalent to 7 mg prednisone, or dexamethasone 6 mg as 'equivalent' to prednisone 40 mg (as used in many studies).

It is noteworthy that the treatment outcome of childhood ALL patients in Indonesia has advanced during the last decade, with increasing 3-year EFS from about 20% in the WK-ALL-2000 protocol to about 37% in the Indonesia-ALL-2006 protocol. Although this achievement can in no way be compared to studies in Western countries that report cure rates of over 80%,[40] our achievement shows that childhood ALL can be treated successfully in a low-income situation such as in Indonesia. This progress illustrates the benefit of our twinning program with the VU University Medical Center (Amsterdam, the Netherlands),[18] which generated research projects and significantly improved our knowledge related to treating childhood cancer.

In an attempt to obtain better outcomes from the Indonesia-ALL-2006 protocol, we recommend to skip the anthracyclines from induction treatment in the SR patients and to continue the randomization of dexamethasone and prednisone during a 3-drug induction for SR patients in an Indonesian multicenter study. Further study may randomize the dose of 40 or 60 mg/m^2 prednisone versus 6 mg/m^2 dexamethasone. Our study supports the opinion advocated by Hunger et al.[41] that developing a protocol in countries with poor supportive care, and where few children are currently being cured, should be performed with extreme caution with regard to potential toxic and drug-related life-threatening complications.

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Conflict of interest

All authors declare that there are no conflicts of interest.

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