CHAPTER 7

L-asparaginase: Long-term Results of a Randomized Trial of the Effect of Additional 3 Doses during Consolidation Treatment in the Indonesian WK-ALL-2000 Protocol

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ABSTRACT

Summary: We conducted a randomized trial to compare the influence of 3 additional doses of L-asparaginase on clinical outcome of newly diagnosed childhood acute lymphoblastic leukemia (ALL). Patients were treated using Indonesian WK-ALL-2000 protocol between 1999 and 2005 and randomized to receive (arm 3A, n=61) or not to receive (Arm 0A, n=56) an additional 3 weekly doses of 6000 U/m^2/dose of *E. coli* L-asparaginase during consolidation treatment on top of 2 doses (standard risk patients) or 5 doses (high risk patients). Events after remission included relapse (37.6%), death (16.2%) and abandonment of therapy (15.4%). There was no significant difference in relapses between the two arms. Patients in Arm 3A versus 0A tended to have a lower 5 years disease-free survival 47.4 ± 7.9% vs. 51.7 ± 7.9% (P=0.72) and lower 5 years event-free survival 29.5 ± 5.8% vs. 35.7 ± 6.4% (P=0.61). We conclude that in our setting the use of three additional doses of L-asparaginase during consolidation therapy did not result in survival advantage. Contrariwise, adverse effects from this drug included higher treatment cost and systemic toxicity.

Key words: L-asparaginase, acute lymphoblastic leukemia, randomized trial, low-income country

Introduction

L-asparaginase is widely used as a standard chemotherapeutic agent for treating acute ALL. It induces plasma asparagine depletion, resulting in leukemic cell death. Based on this mechanism of action and because of its minimal myelosuppressive effect,[1] it is an ideal agent for induction of remission and for treatment intensification. Published studies report conflicting results with L-asparaginase during treatment intensification. Additional, high-dose L-asparaginase administered during intensification as reported from the Dana Faber Cancer Institute,[2] or during continuation treatment in the randomized Italian-Dutch-Hungarian study[3] has deminstrated improved disease-free survival (DFS). However, the Associazione Italiana Ematologia Oncologia Pediatrica Study reported no advantage of protracted, high-dose L-asparaginase administration during re-induction treatment in a BFM-based protocol of intermediate risk ALL children.[4]

In Indonesia we developed a reduced intensity treatment protocol for childhood ALL named WK-ALL-2000,[5] which was implemented in 2000. The clinical trial involved limited use of L-asparaginase, which is the most expensive drug in this protocol. Our objective was to conduct a prospective randomized study to evaluate the benefit of three additional doses of L-asparaginase, during consolidation treatment on the clinical outcome of newly diagnosed patients. Standard risk patients received two doses, while high risk patients received five doses, of 6,000 IU/m^2 each. We used *E. coli* L-asparaginase, the only asparaginase preparation available in Indonesia. In a developing country, the cost of cytostatic drugs, as well as the expense of managing systemic complications arising from intensive treatment regimens, significantly impact on outcome. Eighty per cent of our patients belong to families that earn less than US $ 70 per month.

Materials and methods

Study design and criteria

This was a prospective randomized study, conducted at the Pediatric Cancer Unit of Dr. Sardjito Teaching Hospital (DSH), Universitas Gadjah Mada, Yogyakarta, Indonesia. It involved all newly diagnosed childhood ALL patients entered on the WK-ALL-2000 protocol. Inclusion criteria were age between 0 - 14 years at diagnosis, and previously

untreated with steroids or on other leukemia protocols; parental consent was mandatory. The diagnosis of ALL was confirmed on morphology and cytochemical features of lymphoblasts in marrow samples. Immunophenotypic examination was not routinely available. The following patients were categorized as standard risk: a) age between 1 - 9 years, WBC count less than 50,000/µl, absence of mediastinal mass on chest x-ray, absence of central nervous system (CNS) leukemia (defined as blasts in cerebrospinal fluid obtained by lumbar puncture) and, b) absolute peripheral lymphoblast count less than 1,000/µl on day 8 of induction therapy. All others were stratified as high risk patients.

During the study period March 1999 to June 2005, 211 children newly diagnosed with ALL were admitted to DSH. Twenty-one patients were excluded for the following reasons: previous treatment with steroids or therapy on other leukemia protocols (8), age over 15 years (5), mixed lineage leukemia (4), parents refusal (2), L3 morphology of lymphoblasts per the FAB classification (1), and non-diagnostic marrow morphology (1).

Eight patients were transferred to other protocols after having achieved complete remission (CR). Amongst the remaining 172 patients, 55 (31.9%) were induction failures, 23 (13.4%) died, 21 (12.2%) could not afford treatment, and 11 (6.4%) had resistant/progressive disease. The remaining 117 children were included in this study, and randomized by computer onto either Arm 3A (n=61;52.1%) or Arm 0A arm (n=56; 47.9%).

Treatment protocol

The WK-ALL-2000 protocol[5] was adapted from the Dutch ALL-VI protocol.[6] It consisted of 6 weeks of induction therapy, 4 weeks of consolidation, and a maintenance phase adding up to a total of 2 years of treatment. It uses a 3-drug induction therapy regimen, including dexamethasone (Figure 1). High risk patients are treated with one additional dose of daunorubicin during induction, as well as a re-induction phase that follows consolidation therapy. Otherwise, the protocol remains the same for SR and HR patients. Two, once weekly doses of *E. coli* L-asparaginase 6,000 IU/m^2 iv were given during induction in both risk groups, in addition to which HR patients were given three doses of this drug during re-induction treatment. Patients in Arm 3A received three additional, once weekly, doses of L-asparaginase 6,000 IU/m^2 iv during consolidation therapy. The additional doses of

L-asparaginase were provided by donations from Dutch Estella Foundation, thereby preventing added financial burden to the patients' families.

Outcomes and statistical analysis

Complete remission was defined at the end of induction treatment as the absence of lymphoblasts in peripheral blood and cerebrospinal fluid, less than 5% lymphoblasts in active hematopoetic marrow with no evidence of localized disease anywhere. Relapse was defined as recurrence of lymphoblasts or localized infiltration of lymphoblasts at any site after CR. Disease-free survival was calculated as the interval from the date of achieving CR to date of relapse. The event-free survival (EFS) was calculated as the interval from the date of achieving CR to date of a first event. Events were relapses, death or abandonment to treatment. The observation was closed in July 31, 2010. The EFS and DFS curves were estimated using Kaplan-Meier method and compared using the Mantel-Cox test. A SPSS computer program was used for all analysis and a two-sided *P* value less than .05 was used as level for statistical significance.

Results

Patient characteristics were comparable between the two Arm 0A and 3A, with the exception of a higher WBC count (greater than 50,000/μl) in Arm 0A (Table 1). The first event during remission was relapse in 44 (37.6%), mortality in 19 (16.2%), and discontinuation of treatment in 18 (15.4%) patients (Table 2). There were no significant differences in relapse rates or sites of relapse between the two arms (35.7% in 0A and 39.4% in 3A, *P*=0.37). The median time to relapse after CR was longer in the Arm 3A (22.4 [range: 0.5 - 64.8] months) than in the Arm 0A (10.5 [range: 1.3 - 42.8] months, *P*=0.12). Most relapses (31 or 71%) were isolated hematological relapses. Twenty seven (61.4%) relapses occurred on therapy, especially during maintenance therapy (52.3%). Patients in Arm 0A tended to experience relapses during treatment more often than those in the Arm 3A; these differences, however, did not reach statistical significance.

In our experience, early mortality did not always follow the onset of relapse. Thirty-one (70.5%) of 44 patients who relapsed were confirmed

dead within a median of 3.3 months (range: 1 day - 49.9 months). Five (11.4%) were still alive until the end of the study observation date, with a median of 21.4 months (range: 3.2 – 49.1). Another eight patients were lost to follow-up after completion of treatment, and censored at date last seen.

Patients in Arm 3A versus Arm 0A did not show any statistically significant difference in five year DFS (47.4 ± 7.9% versus 51.7 ± 7.9%, *P*=0.72) or five year EFS (29.5 ± 5.8% versus 35.7 ± 6.4%, *P*=0.61) as depicted in Figure 2 and Figure 3, respectively.

TABLE 1. **Characteristics of patient at diagnosis**

	0A (n=56)		**3A[a] (n=61)**		**Total (n=117)**		***P*-value**
	n	(%)	**n**	(%)	**n**	(%)	
Risk group							0.26
Standard Risk	32	(57,1)	41	(67,2)	73	(62,4)	
High Risk	24	(42,9)	20	(32,8)	44	(37,6)	
Sex							0.44
Boy	31	(55,4)	38	(62,3)	69	(59,0)	
Girl	25	(44,6)	23	(37,7)	48	(41,0)	
Age (years)							0.69
1 - 9	50	(89,3)	53	(86,9)	103	(88,0)	
10 - 14	6	(10,7)	8	(13,1)	14	(12,0)	
WBC (/μl)							0.04
< 50,000	40	(71,4)	53	(86,9)	93	(79,5)	
≥50,000	16	(28,6)	8	(13,1)	24	(20,5)	
Early response at day-8 treatment[b]							0.72
Good responder	49	(87,5)	52	(85,2)	101	(86,3)	
Poor responder	7	(12,5)	9	(14,8)	16	(13,7)	

a, Arm 3A is the group of patients who received 3 additional doses of L-asparaginase during consolidation treatment, arm 0A is the group who did not receive it; **b,** Based on peripheral absolute lymphoblasts count: good responder when less than1000/μl, poor responder when 1000/μl or more.

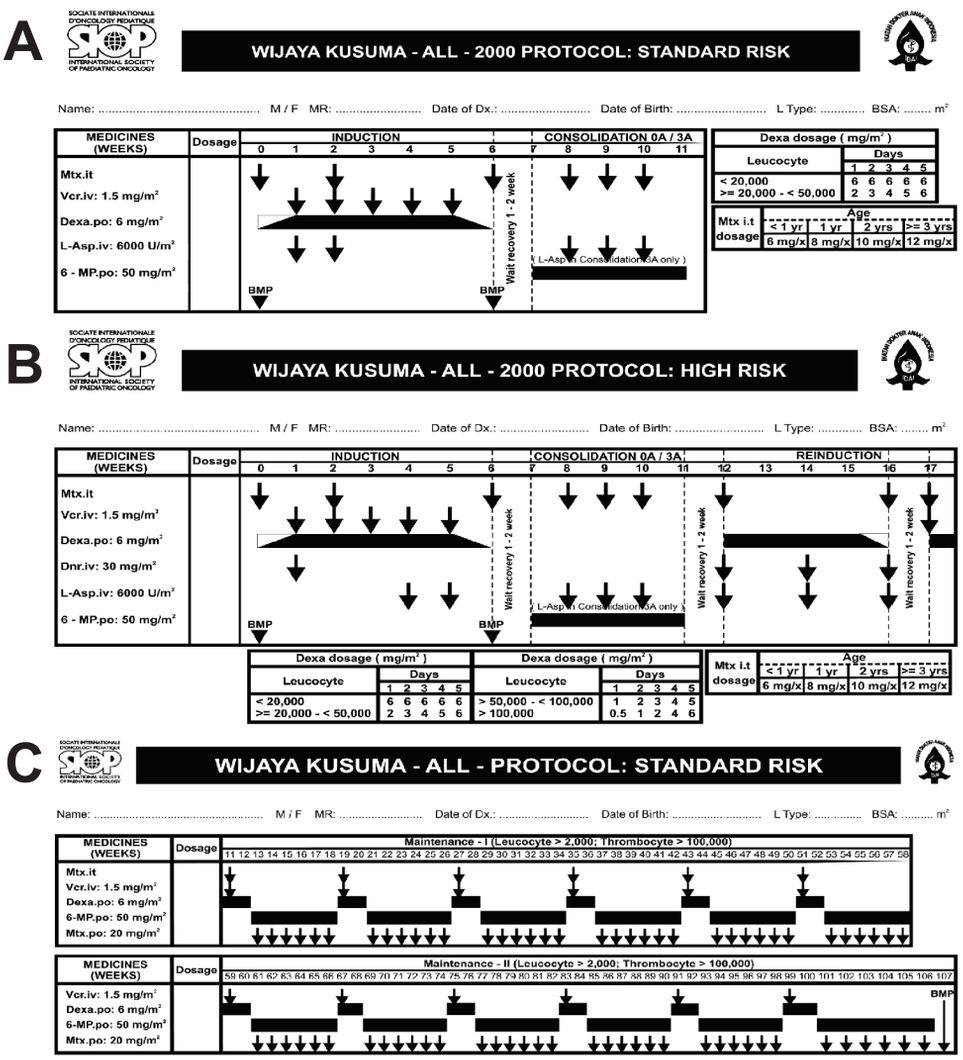

FIGURE 1. **Wijaya Kusuma (WK)-ALL-2000 protocol.** The induction and consolidation treatment for standard risk patients. Only patients in 3A arm received the additional 3 doses of weekly L-asparaginase 6,000 IU/m^2 iv during consolidation treatment **(A)**. High risk patients received additionally one dose of daunorubicin in induction plus a re-induction phase **(B)**. The maintenance treatment was similar between standard risk and high risk patients **(C)**.

TABLE 2. **Clinical outcome during remission**

	0A arm (n = 56)		3A arm (n = 61)		Total (n = 117)		OR	95%CI	*P*-value
	n	(%)	n	(%)	n	(%)			
CR	20	(35.7)	16	(26.2)	36	(30.8)			
First adverse event	36	(64.3)	45	(73.8)	81	(69.2)	1.56[a]	0.71-3.44	0.27[c]
Relapse	20	(35.7)	24	(39.4)	44	(37.6)	1.50[a]	0.62-3.64	0.37[c]
Death	8	(14.3)	11	(18.0)	19	(16.2)	1.72[a]	0.56-5.29	0.34[c]
Abandonment	8	(14.3)	10	(16.4)	18	(15.4)	1.56[a]	0.50-4.88	0.44[c]
Site of relapses									
Isolated hematological	14	(70.0)	17	(70.8)	31	(70.4)			
Isolated CNS	4	(20.0)	4	(16.6)	8	(18.2)			
Isolated testicle	0	(0)	1	(4.2)	1	(2.3)			
Combined	2	(10.0)	2	(8.4)	4	(9.1)			
Treatment phase of relapses									
After completing treatment	5	(25.0)	12	(50.0)	17	(38.6)			
During treatment	15	(75.00	12	(50.0)	27	(61.4)	0.33[b]	0.09-1.21	0.09[c]
Consolidation	1	(5.0)	2	(8.3)	3	(6.8)			
Re-induction	1	(5.0)	0	(0)	1	(2.3)			
Maintenance	13	(65.0)	10	(41.7)	23	(52.3)			

CR, complete remission; OR, odds ratio for arm 3A relative to arm 0A; CI, confidence interval; **a,** ORs for any first event and specific first events during remission (Continuous remission is taken as the reference outcome category); **b,** ORs for relapse occurred during treatment relative to after completing treatment (Relapse after completing treatment is taken as the reference); **c,** Chi-square test.

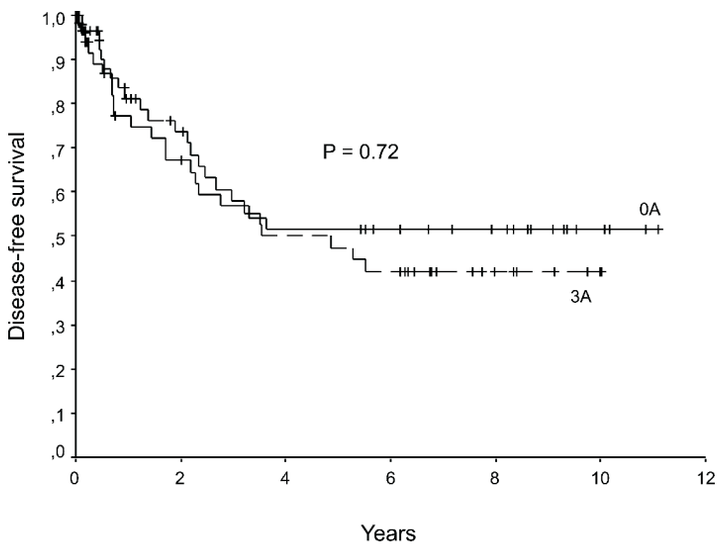

FIGURE 2. **Kaplan-Meier curve for disease-free survival (DFS) by treatment arm.** The Arm 3A is group of patients who received additional 3 doses of L-asparaginase during consolidation treatment, and Arm 0A is group of patients who did not receive it.

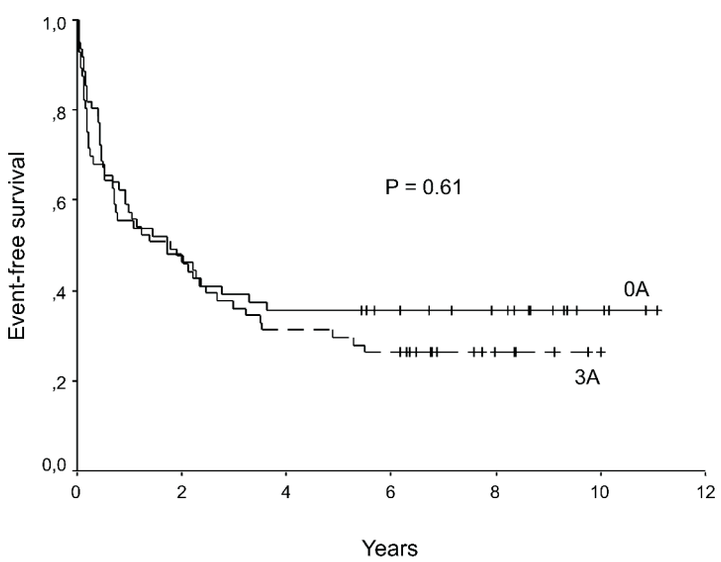

FIGURE 3. **Kaplan-Meier curve for event-free survival (EFS) by treatment arm.**

Discussion

L-asparaginase has been used as an essential component of induction therapy drug regimens in the treatment of childhood ALL for decades.[7] International studies reported the benefit of treatment intensification using L-asparaginase.[3,8] There are 3 types of L-asparaginase: the native form derived from Escherichia coli, a second type from Erwinia chrysanthemi, and the pegylated enzyme form of *E. coli*. Pharmacokinetic comparative studies showed that *E. coli* derived L-asparaginase had a half-life of 1.24 days, that of the Erwinia-derived product was 0.65 days, and that of pegylated *E. coli* was 5.73 days.[9] Dose and schedules for optimal administration of different types of L-asparaginase continue to be defined.[10] In the EORTC-CLG 58881 study, a twice weekly dose of *E. coli* or Erwinia L-asparaginase of 10,000 IU/m^2/dose was administered intravenously for 12 doses in Protocols I and II of a BFM-90 based protocol. The results demonstrated that *E. coli* L-asparaginase was superior to Erwinia L-asparaginase in terms of remission rate, relapse rate and EFS.[11] The Italian-Dutch-Hungarian randomized ALL study in standard risk patients utilized weekly administration of Erwinia L-asparaginase, 25,000 IU/m^2/dose, for 20 doses during continuation therapy. This extended high dose L-asparaginase regimen may have compensated reduced leukemia control resulting from a reduced treatment intensity, thus yielding a better EFS than its complementary group.[3] A Pediatric Oncology Group study of relapsed ALL compared four once-weekly doses, versus two doses every other week, of pegylated L-asparaginase (2,500 IU/m^2/dose); higher remission rates were achieved in the weekly treatment group.[12] Another pharmacokinetic and pharmacodynamic study showed that a 5,000 IU/m^2/dose *E. coli* L-asparaginase given every third day for eight doses during induction in the DCOG-ALL10 protocol was sufficient to yield complete remission in 31 of 32 patients; a minimal residual disease level of less than10^{-4} was detected in 25 of 31 patients.[13] A study comparing L-asparaginase activity after first-time exposure in induction treatment showed no differences between intramuscular and intravenous routes of administration.[14] The outcome and toxicity of intensification using L-asparaginase is influenced by the type of L-asparaginase, as well as by the protocol design. Common side effects of asparaginase include allergic reaction, anaphylaxis, pancreatitis, diabetes

and coagulopathies. In a number of studies, *E. coli* L-asparaginase yielded superior outcomes to Erwinia L-asparaginase, but induced more toxicity. [11,15,16]

Considering the limited availability of L-asparaginase in developing countries, and lack of consensus regarding optimal dosage and route of administration, we chose once-weekly intravenous administration of *E. coli* L-asparaginase 6,000 IU/m^2/dose for two doses only in standard risk patients, and five doses for those in the high risk group. In addition, there was a randomization to three additional doses during consolidation therapy. However, the randomization was not balanced for higher WBC count, resulting in Arm 3A patients having a significantly lower number of patients with higher WBC count.

Notwithstanding the larger number of standard risk patients in Arm 3A, the EFS was lower than in Arm 0A. Further review of data revealed that administration of this drug was delayed, sometimes by several days, because of drug non-availability, side-effects, clinical status of patients, or of error. These situations resulted in a more attenuated intensification regimen than planned in the protocol. Several studies have shown that fewer doses will fail to maintain serum asparagine depletion, thereby leading to inferior outcome.[16,17] We do not have a clear explanation regarding the trend towards a higher death rate in patients who received 3 additional dose of L-asparaginase. It may be explained by a higher number of side effects in Arm 3A; however, this could not be confirmed due to insufficient data capture items pertaining to toxicity. Based on our clinical observation, the adverse effects during L-asparaginase administrations were mostly manifest as dermatological allergic reactions; no anaphylaxis or other severe systemic effects were attributed to the use of L-asparaginase. It is noteworthy that patients who received three additional doses of L-asparaginase tended to have later relapses, often after completing treatment; these events were not noted in those assigned to Arm 0A. However, on Kaplan-Meier analysis, the difference was not found to achieve significance.

Limited resources in our setting did not permit us to test for antibodies to L-asparaginase. As well, we could not ascertain whether cases of T-cell ALL were more prevalent in the group of patients who received additional doses of L-asparaginase, although that is unlikely because WBC counts at diagnosis were lower in Arm 3A (T-cell ALL cases tend to have higher WBC counts).

Factors known to contribute to poor outcomes of childhood ALL in developing countries include treatment-related toxic deaths, lack of adherence to protocol-designed treatment plans, parental discontinuation of treatment, and limited supportive care for treatment-induced systemic toxicity. The WK-ALL-2000 protocol was designed to address these issues by devising a more realistic, less intensive treatment approach appropriate to the situation in Indonesia. Compared with ALL treatment outcomes reported from the United States and Europe indicating complete remission rates in the vicinity of 95%, and 5 year EFS ranging from 65% to 83%,[18-25] the outcome of our WL-ALL-2000 Protocol treatment study at DSH indicates much room for improvement. Problems with compliance contributing to low EFS in Indonesia have been identified by Mostert et al,[26] and Sitaresmi et al.[27,28] They include issues relating to medical staff, patients, families and the influence of socio-economical factors.

We conclude that the use of three additional doses of *E. coli* L-asparaginase during consolidation treatment as scheduled in the WK-ALL-2000 did not result in clinical benefit on long-term follow up. On the contrary, they added to the cost of therapy as well as to toxic drug effects.

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Conflict of interest

All authors declare that there is no conflict of interest.

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