RESEARCH ARTICLE

Relapse-free Rate with Childhood Acute Lymphoblastic Leukemia Treated under the Thai National Protocol

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Abstract

Background: The standard national protocol for treatment of acute lymphoblastic leukemia (ALL) in children was implemented in 2006. A systematic evaluation of the treatment outcome is needed. This study examined the relapse-free survival among childhood ALL cases treated with this protocol and related factors. Materials and Methods: A descriptive study was conducted in children aged between 0-15 years, newly diagnosed with ALL between March 2006 and March 2011 at Srinagarind Hospital, Department of Pediatrics, Faculty of Medicine, Khon Kaen University. The patients were treated on the basis of stratified risk as per the Thai national protocol. Data were compiled from the hospital records. The Kaplan-Meier method was used to describe relapse-free survival and the Cox proportional hazard model to investigate the associated factors. Results: Of the 103 children recruited, 86 (83.5%) achieved complete remission. The total follow-up time was 3132.5 person-months. Eighteen (20.9%) relapsed. The incidence density was 0.6 per 100 person-months (95%CI: 0.4, 0.9). The respective relapse-free rates at 1, 3 and 5 years were 93.0% (95%CI: 85.1, 96.8), 84.5% (95%CI: 74.0, 90.9) and 64.1% (95%CI: 45.6, 77.8). A factor associated with the relapse-free rate was age under 1 year (HR=6.0; 95%CI: 1.1, 33.8). Conclusions: The rate of being relapse-free in ALL children treated under the Thai national protocol at Srinagarind Hospital was better than with former protocols; however, it is still not as good as in developed countries. Further review of the treatment approach of ALL is needed.

Keywords: Acute lymphoblastic leukemia - relapse-free - Thai national protocol

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Introduction

Leukemia is the most common malignancy in childhood. In general, acute lymphoblastic leukemia (ALL) is more common than acute non-lymphoblastic leukemia (ANLL). The incidence of leukemia in Thailand is 38 per million and the respective age-standardised rates (ASR) for ALL and ANLL are 28 and 8.6 per million (Wiangnon, 2011). Currently, ALL has a favourable outcome, as the cure rate is more than 70% (Lanzkowsky, 2011). Before 2006, there was no common protocol for treating ALL in Thailand. The treatment protocol differed at each institution; thus, the reported 5-year overall survival varied between 38.0% and 63.5% (Srivannaboon, 1997; Chainansamit, 2001; Kamsa-ard, 2004; Suesirisawad, 2006). In 2006, Thai Pediatric Oncology Group (ThaiPOG) developed the national guidelines for the treatment of childhood leukemia; both to maintain the international standard and to implement a practicable treatment policy for the country as a whole. The National Health Security Office (NHSO) set a budget for disease management of leukemia/lymphoma guaranteeing nationwide patient access to diagnostics, chemotherapy and hospital support.

Srinagarind Hospital, a supra-tertiary, university hospital located in Khon Kaen, the heart of Northeast Thailand immediately implemented this national protocol for the treatment of childhood ALL. The treatment outcome was to be evaluated by the systematic collecting and analyzing of data. This study was conducted to determine the relapse-free rate and to investigate the factors influencing relapse among childhood ALL treated under the aegis of the Thai national protocol.

Materials and Methods

All relevant records for children under 15, newly diagnosed with ALL between March1, 2006 and March 31, 2011 were retrieved from the data set of the Khon Kaen Provincial Cancer Registry, Cancer Unit, Srinagarind Hospital. The diagnosis of ALL was based on the ICD coding for Oncology (ICD-O-3) (WHO, 2000). The details of treatment were also searched in the medical

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records from the medical record department of Srinagarind Hospital. All of the children treated under the national protocol were included in the study. Children who had their treatment protocol changed were excluded. The follow-up was censored March 31, 2012.

Children with an initial white blood cell count (WBC) <50,000/mm^3, between 1 and 10 years of age and had common ALL by immunophenotype (non-T, non-mature-B cell immunophenotype) were considered as having a standard risk, while those with extreme age (<1, >10), initial WBC >50,000/mm^3, T-cell immunophenotyped, extramedullary organ involvement and abnormal cytogenetic study (positivity of Philadelphia chromosome) were high risk.

The chemotherapy protocol comprises an induction phase (vincristine, prednisolone, L-asparginase, intrathecal methotrexate), a consolidation phase (high-dose methotrexate), a delayed-intensive phase (dexamethasone, vincristine, cyclophospahmide, cytarabine, L-asparaginase) and a maintenance phase (vincristine, 6-MP, methotexate, pulse prednisolone).

Data were recorded twice using Microsoft Access 2007 by 2 independent data entry personnel, verified by STATA/IC 10.0 and corrected in the event of the any disparity. All of the variables were checked for validity, missing data and outliers; then corrected if appropriate.

Data analysis

Descriptive statistics of demographic and clinical characteristics were analyzed using STATA/IC 10.0. The Kaplan-Meier method was used to estimate relapse-free survival. The Cox regression analysis was performed to identify associated factors ($p<0.05$). The factors with a p-value from the Wald test <0.25 and clinically relevant, as per the multivariable analysis by Cox regression were further investigated.

Results

Between March 1, 2006 and March 31, 2011, 103 children under 15 years of age with newly diagnosed ALL were treated at Srinagarind Hospital. Boys predominated (1.7:1). The most common age group was 1-10 years-olds (N=71, 68.9%). The respective mean and median ages at diagnosis were 6.5 (SD 4.2) and 5.8 years (0.3-14.9). Most children (n=79; 76.7%) had an initial white blood cell count (WBC) <50,000/mm^3. The median WBC count was 48,603.3 cell/mm^3. Immunophenotypically, the B-cell type was 86 (83.5%). The majority of patients did not have disease with central nervous system involvement at diagnosis (87.4%). None of the patients had a mediastinal mass nor testicular involvement. Eventually, 61 children (59.2%) were treated using the high risk protocol.

Relapse- free survival

Of the 103 ALL children treated under the national protocol, 86 (83.5%) achieved complete remission after the induction chemotherapy. Of the 17 patients who did not achieve complete remission, 12 died during the induction phase, 3 received alternative treatments or were referred to another hospital, and 2 had a partial response.

Of the total group of patients (103 cases), 3132.5 person-months of time were at risk with an incidence density of 0.6 per 100 person-months (95%CI: 0.4, 0.9). Eighteen patients (20.9%) relapsed (Figure 1A). The relapse-free rates by sex, age, treatment protocol, ALL subtype, initial WBC and CNS involvement at diagnosis are present in Figures 1B, 1C, 1D, 1E, 1F and 1G.

The respective relapse-free rate at 1, 3 and 5 years was 93.0% (95%CI: 85.1, 96.8), 84.5% (95%CI: 74.0, 90.9) and 64.1% (95%CI: 45.6, 77.8) (Table 1).

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Associated factors for risk of relapse-free rate (Table 2)

The respective median time to relapse in childhood ALL in infants <1 year, >10 year, high risk group, T-cell type and CNS involvement at diagnosis were 39.6, 54.3, 55.5, 54.3, 54.3 months. Meanwhile, the relapsed-free rates for both sexes, aged between 1 and 10 years, standard risk, B-cell type, initial WBC (>50,000/mm^3) and no CNS involvement, were all >50% at all time points (Table1).

The relationship between each of the independent variables and relapse-free survival were analyzed. The bivariate analysis revealed that both sexes had a similar relapse-free rate (HR=1.1; 95%CI: 0.4, 3.0; p-value 0.81). Notably, infants and children older than 10 years had a higher respective relapse-rate 10.9 and 3.1 times more than children between 1and 10 years of age (95%CI: 2.7, 43.1; p-value <0.01 and 95%CI: 1.1, 8.0; p-value 0.03). The children classified as having a high risk had a significantly higher rate of relapse (2.8 times more) than those with standard risk (95%CI: 1.0, 7.8; p-value 0.05). The immunophenotype (T or B cell precursor) and initial

Table 1. Median Time to Relapse and Probability of Relapse-free at 1, 3 and 5 Years

Variable	Median time to relapse Months (95%CI)	Proportion of relapsed -free (%) (years) 1	3	5
Sex				
Male	**	90	86.1	70.6
Female	**	94.6	83.6	58.3
Age (year)				
1-10	**	96.7	90.6	73.3
<1	39.6 (4.8, 39.6)	60	60	***
>10	54.3 (24.6,*)	90	70.1	46.7
Treatment protocol				
Standard risk protocol	**	94.9	91.7	80.2
High risk protocol	55.5 (39.6,*)	91.5	77.9	48.2
ALL subtype				
ALL, precursor T-cell	54.3 (54.3,*)	84.6	84.6	***
ALL, precursor B-cell	**	94.5	84.7	67.2
initial WBC (mm^3)				
<50,000	**	94.2	86.9	65
>50,000	**	88.2	73.5	63
CNS involvement				
No	**	94.7	86.8	75.8
Yes	54.3 (29.7, 55.3)	80	68.6	18.3

* 95%CI not available due to sample size limitation. ** Median time to relapsed not available due to number of relapse < 50%. *** Relapse-free rate not available due to sample size limitation

Table 2. Number of Patients and Risk Factors for the Relapse-free Rate

Variable		N	Relapse	Person -times	IR/100 person-months (95%CI)	Bivariate analysis HR_{crude}(95%CI)	p-value	Multivariate analysis HR_{adj}(95%CI)	p-value
Sex	Male	30	6	1093	0.5 (0.2; 1.2)	1		-	-
	Female	56	12	2039.5	0.6 (0.3; 1.0)	1.1 (0.4; 3.0)	0.81	-	-
Age (year)	1-10	61	9	2474.5	0.4 (0.9; 0.7)	1		1	
	<1	5	3	90.5	3.3 (1.1; 10.3)	10.9 (2.7; 43.1)	<0.01	6.0 (1.1; 33.8)	0.04
	>10	20	6	567.5	1.1 (0.5; 2.4)	3.1 (1.1; 8.9)	0.03	2.2 (0.6; 8.6)	0.24
Treatment protocol	Standard risk protocol	39	5	1603.1	0.3 (0.1; 0.7)	1		1	
	High risk protocol	47	13	1529.4	0.9 (0.5; 1.4)	2.8 (1.0; 7.8)	0.05	1.1 (0.3; 5.3)	0.79
ALL subtype	ALL, precursor: T-cell	13	3	376.4	0.8 (0.2; 2.5)	1		1	
	B-cell	73	15	2756.1	0.5 (0.3;0.9)	0.7 (0.2; 2.4)	0.56	1.1 (0.3; 4.6)	0.85
initial WBC (mm^3)									
	<50,000	69	13	2578.8	0.5 (0.3;0.9)	1		1	
	>50,000	17	5	553.8	0.9 (0.4; 2.1)	1.8 (0.7; 5.2)	0.25	1.2 (0.3; 4.5)	0.76
CNS involvement	No	76	12	2788	0.4 (0.2; 0.8)	1		1	
	Yes	10	6	344.6	1.78 (0.8; 3.9)	3.7 (1.4; 9.9)	<0.01	2.1 (0.6; 6.6)	0.23

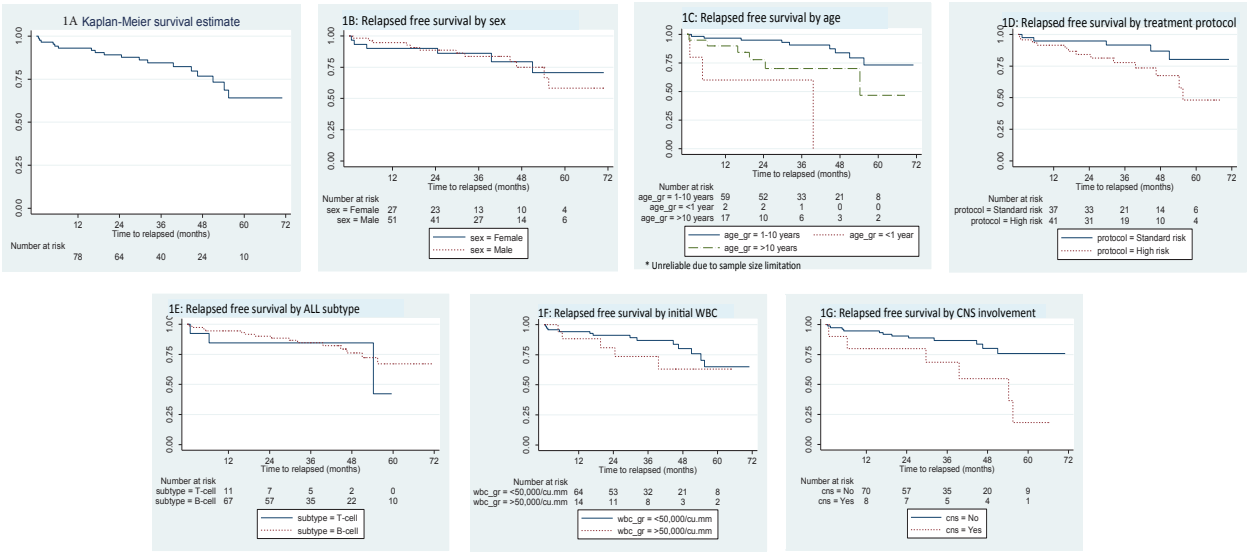

Figure 1. Overall Relapsed Free Rate and Associated Factors

WBC (more or less than 50,000/mm^3) were not significant risk of relapse (HR=0.7; 95%CI: 0.2, 2.4; p-value 0.56 and 95%CI: 0.7, 5.2; p-value 0.25) By contrast, CNS involvement at diagnosis indicated a potential 3.7 times greater risk of relapse than those without CNS disease (95%CI: 1.4, 9.9; p-value <0.01).

According to multivariate analysis, of all of the variables with a p-value of <0.25 according to the Wald test and clinically relevant factors (age, WBC at diagnosis, CNS disease), the only adversely associated factor for the relapse-free rate was age under 1 year (HR=6.0; 95%CI: 1.1, 33.8).

Discussion

Leukemia is the most common malignancy in childhood ; of the two types acute lymphoblastic leukemia (ALL) is more common than acute non-lymphoblastic leukemia. At present, ALL has a very favorable outcome especially for the low risk variant. The cure rate is more than 80% in resource-rich countries (Lanzkowsky, 2011). Before 2006, there was no common protocol for treating ALL in Thailand. The treatment protocol differed at each hospital which resulted in a highly variable 5-year overall survival (between 38.0% and 63.5%) (Srivannaboon, 1997; Chainansamit, 2001; Kamsa-ard, 2004; Suesirisawad, 2006). Since 2006, the same national protocol has been used according to the guidelines proposed by the Thai Pediatric Oncology Group (ThaiPOG). In addition, the National Health Security Office (NHSO) has been providing the budget to cover all the costs of treatment which has meant full medical access for all people. We have implemented the national protocol to treat all childhood ALL since its introduction. Apart from initial WBC and age at diagnosis (as used in the former risk stratification), immunophenotyping of leukemic cell assessed by flow cytometry was also used to stratify risk.

Age and sex distribution of patients, T and B immunophenotyping of leukemic subtype were similar to the studies in ALL patients across Thailand and other countries. (Chainansamit, 2001; Suesirisawad et al., 2006; Moghrabi et al., 2007; Khalid et al., 2010; Silverman et al., 2010). According to the risk stratification by the Thai national protocol, the ratio of patients with high risk to low risk was notably higher than that observed in several studies (Long et al., 2008; Hazar et al., 2010). This stratification might not represent the true risk as

defined in other study since the molecular study was not included in this study. Therefore, some patients defined as low risk might have been at intermediate or high risk. The number of patients who achieved complete remission was additionally lower than several studies (Moghrabi et al., 2007; Long et al., 2008; Khalid et al., 2010; Hazar et al., 2010). Interestingly, deaths occurring early during the induction phase of chemotherapy was significantly higher among patients treated with the high risk protocol (11.5%). This may indicate the treatment related mortality of intensive chemotherapy.

The 5-year relapsed-free rate in the current study (64%) was lower than in developed nations where it was >80% (Moghrabi, 2007). This outcome is actually similar to reports from China (49.9 %) (Long, 2008) and Turkey (63.2%) (Hazar, 2010). This relapsed-free rate is, nevertheless, superior to the former non-standardized approach used which varied between 21-24% (Srivannaboon, 1997; Suesirisawad, 2006).

The most significant factor affecting the relapse-free rate in this study was the infant < 1 year as mentioned in most studies (Moghrabi et al., 2007; Khalid et al., 2010; Silverman et al., 2010). The possible risks were (a) children aged older than 10 years and (b) those with a CNS disease at diagnosis (Bajel et al., 2008; Silverman et al., 2011). Immunophenotype did not significantly affect the relapse-free rate as in other studies (Gupta et al., 2011). It may be that patients with high risk disease had a greater chance of disease recurrence; however, our risk stratification criteria were not strictly clarified since the molecular abnormalities of the host were not included. Our risk stratification was based on conventional criteria (age, initial WBC and CNS disease); however, we also included the immunophenotyping of blast cells. The relapse-free rate in this study of patients with a low risk was seems conspicuously low. With more sophisticated laboratory results, some of these patients might not have been classed as low-risk. Generally, to achieve a good outcome for ALL treatment, prolonged and adequate chemotherapy is needed. The other factors that may have contributed to the low relapse-free rate in our population were poor compliance and adherence to the chemotherapy.

In conclusion, the relapse-free rate in this study was relatively low compared to resource-rich nations. The high number of early deaths may have resulted from insufficient supportive care. Compliance to chemotherapy and improvement of supportive care should be encouraged and further research in the protocol continued.

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