Treatment Outcomes of Acute Lymphoblastic Leukemia in both children and adults using the Thai Pediatric Oncology Group-based protocol at Chiang Mai University hospital

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Abstract

Backgrounds: Acute lymphoblastic leukemia (ALL) occurs in both children and adults. It is the most common type of cancer in children and its prognosis is not optimistic in adults. According to the advent of effective ALL therapy, long-term survival rates and cured rates could be more than 80%. However, that in Thailand between 1995 and 2009 ranged from 51–59%.

Objective: This study analyses the outcomes of the National Health Security Office (NHSO) ALL national protocols in Thai children and adults, using data collected from the Chiang Mai Cancer Registry, Faculty of Medicine, Chiang Mai University.

Materials and methods: Participants were 83 children and 54 adult patients with ALL between 2005 and 2012. The newly-diagnosed high-risk patients might have been received prophylactic cranial irradiation (PCI). The demographic, clinical char-

acteristics, treatment outcomes, incidence and site of relapse were analyzed using descriptive statistics. The analyses were separated into two parts between children and adults ALL patients: estimated disease-free survival (DSF) and the relapse rates using Kaplan-Meier method and compared the relapse rates in adults using log-rank test.

Results: The five-year overall survival rate for children was 59.04% (45.65% in the high-risk and 70.27% in the standard-risk groups) and for those who relapsed was 21.69% (26.09% and 12.22%, respectively). The five-year DFS rates were 62.6% and 81.2% in the high-risk and standard-risk groups, respectively. In adults, the five-year survival rate was 25.93% and it was 46.30% in those who relapsed, and the five-year DFS rate was 36.2%. The most relapses occurred in central nervous system (CNS).

Conclusion: The standard national protocols for ALL could not improve the outcomes. The relapse occurrence of ALL was still quite common in both children and adults. PCI has been shown a slightly better outcome in terms of prevention or delayed CNS relapse.

Keywords: Acute lymphoblastic leukemia, Chiang Mai Cancer Registry, outcomes, ThaiPOG,

Introduction

In 2012, the International Agency for Research on Cancer estimated that 351,965 new leukemia cases were diagnosed (age–standardized incidence rate [ASR] = 4.7) and 265,471 people died from leukemia (ASR=3.4) globally. While in Thailand, leukemia is the fifth most common cancer in males and the eighth most common in females with 3,744 new cases (ASR = 5.1) and 3,071 deaths (ASR = 4.0).[1] Acute lymphoblastic leukemia (ALL) usually progresses rapidly and is likely fatal within weeks or a few months if a patient is not treated.[2–3] The rate of ALL incidence is approximately 1 to 1.5 per 100,000 persons and exhibits a bimodal age distribution, with the first peak in children aged 4 to 5 years (4 to 5 per 100,000) followed by a second peak at around 50 years of age

(2 per 100,000).[4–5] ALL is the most common cancer in children and accounts for around 80% of children with leukemia.[6–9]

Due to the effectiveness of ALL therapy, the complete remission (CR), disease-free survival (DFS), long-term overall survival (OS), and cured rates have reached more than 80% in children[6–8,10–12]. However, the prognosis in adults is still inferior to children,[9, 13] with a long-term DFS rate of less than 39-40%,[6, 14–15,16] and a cured rate of only 50%.[1] There are some differences between children and adults in the clinical and biological characteristics which have resulted in differences in the types of cancer, metastasis, treatment, and response to treatment. Therefore, analyses of children (age <15) and adults should be separated.

Most treatment failures for ALL remain relapse, which occurs 15–20% of children,[18] in one-third of adults with a standard risk of ALL, and two-thirds of adults with a high risk of ALL.[17] Most relapses occurred in the bone marrow (BM), either in an isolated form or combined with the involvement of another site, mainly central nervous system (CNS) or the testes; isolated CNS or testicular relapse or, much less frequently, relapse involving other extramedullary sites might also occur.[10, 17–19] The site of the relapse and the duration of the first complete remission have influenced on both DFS and OS in children.[18]

The treatment of ALL is chemotherapeutic agent in combination with medication to treat complications, including blood and blood components, which can be required for up to three years.[20] The treatment affects the vital organs of the body, including the liver, kidney, heart, brain, etc. Some patients require radiotherapy to prevent or treat CNS diseases or improve outcome of children with T-cell ALL.[21,22] In adult, PCI is performed in highly aggressive (Philadelphia-chromosome positive) ALL.[23] Now prophylactic cranial irradiation (PCI) has been recently replaced by other treatment strategies (e.g. intrathecal and systemic chemotherapy) because of its association with long term toxicities in ALL survivors,[22] such as learning disability,[24] late neurocognitive sequelae,[24–25] endocrinopathy,[26] and secondary cancers.[27–28] It also psychologically, socially, and economically affects the patients' family members.

Thailand has different protocols among the various institutions caring for leukemia patients[29–30]. To standardize the

treatment of leukemia, the Thai Pediatric Oncology Group (ThaiPOG) proposed a package of national protocols for childhood leukemia treatment in 2006 to the National Health Security Office (NHSO) of Thailand.[20] The protocols were sub-classified according to the subtype of leukemia and the clinical risk factors that had international acceptance and reproducibility: age and initial white blood cell (WBC) count at diagnosis, and new patients were treated according to the new protocols starting in March 2006.[31] Treatment of ALL in adults has largely been based on the adaptation of pediatric regimens, but the success rate has been considerably lower than in children.[32–33]

Herein, we report the outcomes of the NHSO ALL national protocols in Thai children and adults, using data collected from the Chiang Mai Cancer Registry, Faculty of Medicine, Chiang Mai University.

Materials and Methods

Patients

We performed a retrospective analysis of patients who had been diagnosed with ALL at Maharaj Nakorn Chiang Mai Hospital between 1 January 2007 and 31 December 2012. The data were collected by the Chiang Mai Cancer Registry, Faculty of Medicine, Chiang Mai University, which is a population-based cancer registry that collects the data on many types of cancer, including ALL.[34]

Treatment

The child ALL patients (0–15 years of age) were treated by applying the Thai national protocols. The selection of the appropriate protocol was carried out according to stratified risk factors. Thai national protocol ALL-01-05 (standard-risk ALL) was used for patients ranging 1–10 years of age with an initial WBC < 50,000/mm3. Protocol ALL-02-05 (high-risk ALL) was used for patients > 10 years or < 1 year of age with (a) an initial WBC > 50,000/mm3, (b) CNS or testicular disease at diagnosis, (c) T-cell ALL, and/or (d) the specific abnormal chromosome. Protocol NHL-04-06 was used for patients with Burkitt-type acute lymphoblastic leukemia (L3 morphology).[20] For adult ALL, the patients were also treated by modified Thai national protocols.

Variables

Demographic and clinical characteristics were extracted from the medical records, including gender, age at diagnosis, level of education, occupation, number of

family members, anemia, weight loss, fever, fatigue, lymphadenopathy, hepatomegaly, splenomegaly, bone pain, dyspnea, immunophenotype, RBC, WBC, blood platelets, prognosis, and family cancer history.

Ethical approval and consents of patients

This study received ethical from Faculty of Medicine, Chiang Mai University Ethics Committees.

Statistical analysis

All patients were followed up until January 2018. The demographic and clinical characteristics of the patients, treatment outcome and site of relapse were analyzed using descriptive statistics. Death was defined as all-cause mortality; relapses were defined on the basis of morphologic evidence of leukemia in the BM or other sites; OS was defined as the time from either the date diagnosis or the started treatment until death or the end of study; DFS was defined as the time from diagnosis to the event; and events were defined either as relapse or death. Differences in outcome distribution between the risk groups for the child patients were tested using the log-rank test. Due to the difference in the clinical and biological characteristics of ALL between children and adults, the analyses in our study were separated into two parts: the Kaplan-Meier method was used to estimate DFS and the relapse rate, and the differences in the relapse rate in adult patients were tested using the log-rank test to evaluate the results of receiving PCI. All statistical analyses were performed using STATA version 13.

Results

A total of 155 patients were enrolled, 18 of whom were subsequently excluded because of a revised diagnosis of acute myelogenous leukemia (one case), relapse (three cases), denial of treatment with chemotherapy and radiation to the brain (13 cases), and not treated with chemotherapy (one case). Therefore, the data on 137 patients with newly diagnosed ALL were included in the analyses.

All patients had received chemotherapy, and 57 of them were assigned to receive PCI with the prescribed total radiation dose of 18–36 Gy. The median duration of follow-up was 3.41 years (range: 7 days to 11 years).

The characteristics of child patients

We enrolled 83 children with ALL, with boys being more common than girls (1.5:1). The median age at diagnosis was 4 years. Four (4.82%) were classified as T-cell lineage immunophenotype, while one (4.55%) and two (5.56%) were recorded as having a history of HIV history and a family history of cancer, respectively. The median initial WBC was 12,800/mm3 (range: 1,400–515,000/mm3). Characteristics are summarized in **Table 1**. Overall, more than half of the children (n = 46) were categorized in the "high-risk" group. Among these, 80.43% (n = 37) were assigned to receive PCI with a prescribed total radiation dose of 18–36 Gy.

The results of the treatment of the child ALL patients

These results are reported in **Table 2**. The death rates showed no statistically significant difference between the standard-risk and high-risk ALL groups (16.22% vs. 13.04%). The common causes of death include ALL and uncontrolled brain metastasis (8.70% in the high-risk and 16.22% in the standard-risk ALL groups). The OS rate was 85.54% with a median survival time of 69.87 months (86.96% with median 62.18 months and 83.78% with median 84.83 months in the high-risk and standard-risk ALL groups, respectively, p = 0.004). The five-year survival rate of the child patients was 59.04% (45.65% in the high-risk and 70.27% in the standard-risk ALL groups, p = 0.023). In the high-risk ALL group, 62.16% of patients who received PCI survived with controlled brain metastasis, while those who did not receive PCI survived with controlled brain metastasis only 22.22%.

Of the 21.69% child ALL patients who relapsed, 26.09% were in the high-risk and 12.22% were in the standard-risk ALL groups. Relapses of child ALL patients were mostly isolated in the CNS (21.74% and 8.11%), while other relapses were 4.35% and 8.11% in the high-risk and standard-risk groups, respectively. The median survival time of the relapsed patients was 40.57 months (medians of 38.25 months (n = 12) and 43.20 months (n = 6) in the high-risk and standard-risk ALL groups, respectively). About Thirty-three percent (n = 6) of the relapsed patients died (three were high-risk ALL patients). Among the 18 relapsed patients, 10 had received PCI (all of them were high-risk ALL patients), and eight had not (two of them were high-risk ALL patients). The median duration of relapse was 37.43 months. The five-year DFS rates

Table 1. Demographic and clinical characteristics of the patients who received PCI to those who not received PCI

Characteristics	Children		Adults
	Number (%)/Median (IQR)		Number (%)/Median (IQR)
	Standard risk group (n = 37)	High risk group (n = 46)	(n = 54)
Gender			
Male	24 (64.86%)	26 (56.52%)	29 (53.70%)
Female	13 (35.14%)	20 (43.48%)	25 (46.30%)
Age at diagnosis (years)	3.0 (2.0 – 5.0)	6 (4.0 – 10.0)	24 (17.0 – 40.5)
HIV history/34,31			
yes	-	1 (4.55%)	-
no	27 (100.00%)	21 (95.45%)	23 (100.00%)
Cancer history of relatives or family members/47, 37			
Yes	1 (5.88%)	1 (5.26%)	4 (23.53%)
No	16 (94.12%)	18 (94.74%)	13 (76.47%)
Immunophenotype/7, 3			
T-cell	-	4 (10.00%)	7 (13.73%)
B-cell	36 (100.00%)	36 (90.00%)	44 (86.27%)
WBC at diagnosis (mm^3)/-,1	5,520 (3,820 – 16,442)	23,800 (6,891 – 86,257)	21,100 (5,200 – 117,000)

/missing value of children and adult patients, respectively.

Table 2. The Treatment Results of the Child and Adult ALL patients

ALL Treatment Results	Children		Adults (n = 54)
	High Risk (n = 46)	Standard Risk (n = 37)	
Death	6 (13.04%)	6 (16.22%)	15 (27.78%)
ALL	4 (8.70%)	6 (16.22%)	14 (25.93%)
Complications	1 (2.17%)	-	-
Other causes	1 (2.17%)	-	1 (1.85%)
Relapse	12 (26.09%)	6 (16.22%)	25 (46.30%)
Central nervous system (CNS)	10 (21.74%)	3 (8.11%)	21 (38.89%)
Bone marrow (BM)	-	3 (8.11%)	2 (3.70%)
CNS+BM	1 (2.17%)	-	-
Acute myelogenous leukemia (AML)	1 (2.17%)	-	-
Acute promyelocytic leukemia (APL)	-	-	1 (1.85%)
Testes	-	-	1 (1.85%)

were 62.6% and 81.2% in the high-risk and standard-risk ALL groups, respectively **(Figure 1(a)).**

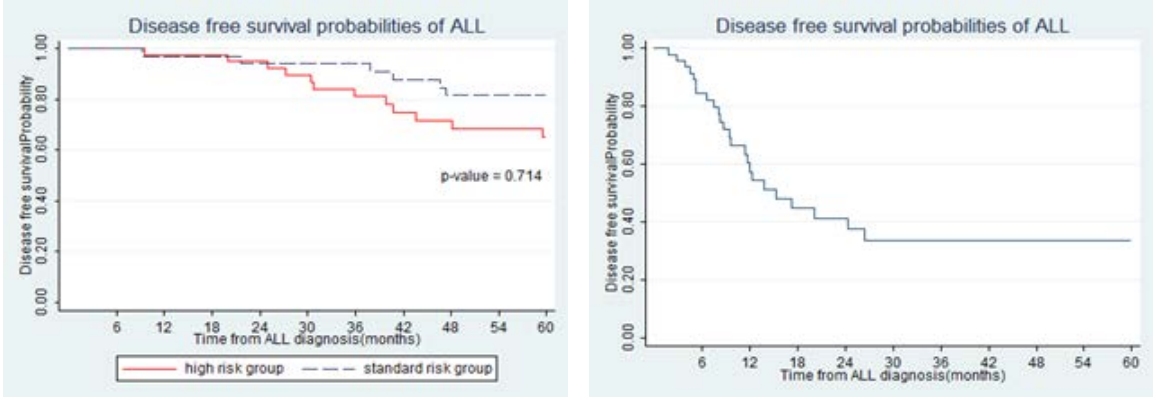
The characteristics of the adult ALL patients

We enrolled 54 adults with ALL. The median age at diagnosis was 24 years. Seven patients (12.89%) were classified as T-cell lineage immunophenotype and four patients (7.41%) as having a family history of cancer. The median WBC, RBC, and platelet count at diagnosis were 21,100/mm3, 9.2 g/dL and 64,250 /mm3, respectively. Characteristics are summarized in Table 1. Among these, 37.04% (n = 20) were assigned to receive PCI with a prescribed total radiation dose of 18–36 Gy.

The results of the treatment of the adult ALL patients

These results are reported in Table 2. The death rate was 27.78%, most of which were due to ALL and uncontrolled brain metastasis (25.93%). The overall and five-year survival rates were 72.22% and 25.93%, respectively, with a median survival time of 26.17 months.

Of the 46.30% adult ALL patients who relapsed, the median duration of relapse was 9.53 months and the five-year DFS rate was 36.2% **(Figure 1(b))**. Relapses in adult ALL patients were mostly isolated in the CNS (38.89%), while other relapses comprised 7.41%. The five-year survival rate of the relapsed patients was 2.5%. The median survival time of relapsed patients was 15.43 months. The five-year overall relapse rates of adult patients was relative high but not related to whether PCI was administered (no PCI: 66.4% and with PCI: 63.8%, p = 0.396) **(Figure 2)**. However, the patients who received PCI had a slightly better outcome in terms of prevention or a delay in CNS relapse (median duration of CNS relapse = 8.23 months in patients with no PCI vs. 11.93 months in patients with PCI) and a longer survival time (median survival time = 21.75 months in patients with no PCI vs. 48.29 months in patients with PCI). Furthermore, 35.0% of patients who received PCI survived with controlled brain metastasis compared to only 20.59% in who did not.



(a) (b)

Figure 1. The ALL Disease free survival rates of (a) child and (b) adult patients who received PCI or did not.

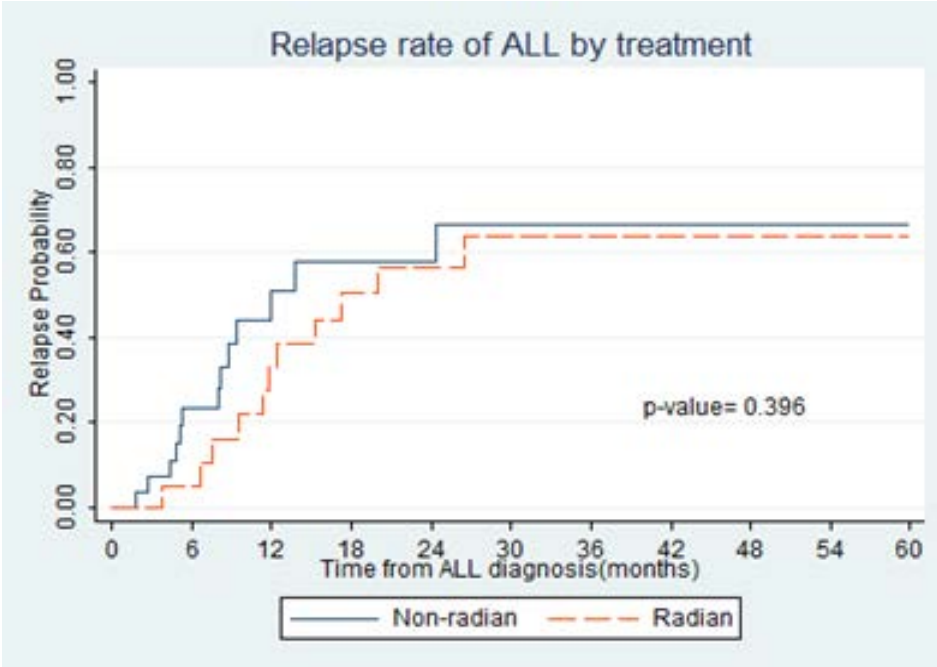


Figure 2. The ALL relapse rates of adult patients who received PCI (Radian) or did not (Non-radian).

Discussion

The survival rate of child ALL patients in developed countries varies from 60–90%, while that in Thailand between 1995 and 2009 ranged from 51–59%.[29] In 2006, ThaiPOG via the NHSO developed the national guidelines for the treatment of childhood leukemia to meet the international standard and implement a practical treatment policy for the country as a whole. The five-year survival of child ALL patients in Khon Kaen between 1985 and 2009 rose to 51% after implementation of the national protocol in 2006.[35] In this study, the five-year survival of ALL patients after implementing the NHSO protocol at the Department of Pediatrics, Chiang Mai University Hospital tended to improve (59.04% overall, 45.65% in the high-risk and 70.27% in the standard-risk ALL groups) and was better than or comparable to previous studies, albeit this outcome is still less than that in developed countries.[34, 36] This accords to the findings of Seksarn[37] and Wiangnon[38], who concluded that survival subsequently improved in patients in the standard-risk ALL group but not in the high-risk one. In

our study, 21.69% of child ALL patients relapsed, which corresponds to previous studies,[18–19, 22] thus it is not certain whether the nationwide implementation of the standard protocols has been beneficial.[31] Recurrence occurred in the high-risk group approximately twice as often as the standard-risk group, resulted in five-year DFS rates of 62.6% and 81.2%, respectively, which is better than the results reported by Seksarn,[31] in which the event free survival rates from 12 institutions throughout Thailand were 51.2% and 66.5%, respectively. Finally, 62.16% of patients who received PCI survived with controlled metastasis.

For the adult ALL patients, the five-year survival rate was 25.93%, which is considered as relatively low compared to previous studies that reported 25–47%.[33, 38–40] Relapse developed in 46.30% of adult ALL patients and the five-year DFS rates was 36.2%, which is similar to the results in for adults diagnosed with ALL from 2005 to 2015 at a reference center in Mexico.[33]

In this study, the relapse occurrence of ALL was still quite common in both child and adult ALL patients and were higher than in previous studies.[11, 17, 19, 41] The majority of relapse occurrence in this study was due to CNS relapse (14 (77.78%) out of 18 relapses in children, and 21 (87.50%) out of 24 relapses in adults). The relatively high rate of CNS relapse in our study might have been related to inadequate systemic chemotherapy[42] and most enrolled patients were high risk of relapse in the CNS or at other sites.[24, 41–42, 43]

There was no difference in the frequency or site of relapse between patients who received PCI and those who did not. However the trend in the rate of CNS relapse was not significantly different, although the patients who received PCI had a slightly better outcome in terms of prevention or delayed CNS relapse. Retrospective data was used in this study and unfortunately, some useful demographic variables were not available for our analysis. Future research with alternative data sources could address the possible relationship between other covariates and relapse occurrence. A study of adolescents and young adults might be useful since the ALL occurring in this age group could be biologically different from that in younger and older ALL patients, and an understanding of the biology of ALL in all of these patient groups could help to improve outcomes and prognosis. The limitation of this study are that its based

on a retrospective analysis. Therefore, in the next study should be added toxicities of pirarubicin in the treatment of childhood acute lymphoblastic leukemia.

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