RESEARCH ARTICLE

Outcome of Childhood Acute Lymphoblastic Leukemia Treated Using the Thai National Protocols

Panya Seksarn[1]*, Surapon Wiangnon[2], Gavivann Veerakul[3], Thirachit Chotsampancharoen[4], Somjai Kanjanapongkul[5], Su-On Chainansamit[6]

Abstract

Background: In recent decades, the prognosis for childhood leukemia has improved, especially for acute lymphoblastic leukemia (ALL). In Thailand, though, the survival rate for ALL is unimpressive. In 2006, standard national protocols for childhood leukemia treatment were implemented. We herein report the outcome of the ALL national protocols and explanations behind discrepancies in outcomes between institutions. Materials and Methods: Between March 2006 and February 2008, 486 children with ALL from 12 institutions were enrolled in the Thai national protocols. There were 3 different protocols based on specific criteria: one each for standard risk, high risk and Burkitt's ALL. We classified participating centers into 4 groups of institutions, namely: medical schools in Bangkok, provincial medical schools, hospitals in Bangkok and provincial hospitals. We also evaluated supportive care, laboratory facilities in participating centers, socioeconomics, and patient compliance. Overall and event-free survival were determined for each group using the Kaplan Meier method. Statistical differences were determined using the log-rank test. Previous outcomes of Thai childhood ALL treatment between 2003 and 2005 served as the historic control. Results: Five-year overall survival of ALL treated using the Thai national protocol was 67.2%; an improvement from the 63.7% of the 12-institute historical control (p-value=0.06). There were discrepancies in event-free survival of ALL between centers in Bangkok and up-country provinces (69.9% *vs* 51.2%, p-value <0.01). Socioeconomics and patient compliance were key elements in determining the outcome (65.5% *vs* 47.5%, 59.4% *vs* 42.9%) (p-value < 0.02). Conclusions: Implementation of standard national protocols for childhood leukemia in Thailand did not significantly improve the outcome of ALL. Factors leading to better outcomes included (a) improvement of treatment compliance (b) prevention of treatment abandonment and (c) financial support to the family.

Keywords: Acute leukemia - children - national protocols - Thailand

Asian Pac J Cancer Prev, **16 (11)**, 4609-4614

Introduction

A survey between 2003 and 2005 of the incidence and survival rate of childhood cancer in Thailand by the Thai Pediatric Oncology Group (ThaiPOG) showed that newly diagnosed childhood cancers per year were around 1,000 cases while the incidence was 76.7 per million children. The incidence in a long-term population-based cancer registration in Khon Kaen registry (1985-2009) was 83 per million children (Wiangnon, 2014). Annually, new cases of acute leukemia were about 700; of which 500 were acute lymphoblastic leukemia (ALL). The five-year overall survival of ALL from the whole country was 64.9 percent (Wiangnon et al., 2011). This overall survival rate is less than in developed countries, but Thailand has different protocols among the various institutions caring for leukemia treatment (Hunger et al., 2012; Allemani et al., 2015).

In order to standardize treatment of leukemia, the ThaiPOG proposed a package of national protocols for childhood leukemia treatment in 2006 to the National Health Security office (NHSO) of Thailand. Protocols were sub-classified according to the subtype of leukemia and clinical risk factors of patients at presentation (Stanulla, 2009). New patients were enrolled to the new protocols starting in March 2006. Herein we report the outcomes of these ALL national protocols in Thai children compared to the historical control. Also studied were the factors influencing outcomes and comparisons of outcomes among the different groups of institutions.

*[1]Division of Hematology/Oncology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, [3]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, [5]Queen Sirikit National Institute of Child Health, Bangkok, [2]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, [6]Department of Pediatrics, Khon Kaen Hospital, Khon Kaen, [4]Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand *For correspondence: py_seksarn@yahoo.com*

Materials and Methods

Patients and hospital group

Between March 2006 and February 2008, all newly diagnosed ALL patients between 0 and 15 years of age from the 12 institutions throughout Thailand were enrolled for treatment using the Thai national protocols. The selection of the appropriate protocol was done according to stratified risk factors. All patients were followed up until December 2011.

The participating centers in the study included: 5 in Bangkok (the capital), 4 in the northeastern region, 2 in the northern region and 1 in the southern region. These centers were classified into 4 groups: (a) medical schools in Bangkok (n=4), (b) provincial medical schools (n=3), (c) hospitals in Bangkok (n=1) and (d) provincial hospitals (n=4).

Treatment

Thai national protocol ALL-01-05 (standard risk ALL) was used for patients between 1 and 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 or (a) an initial WBC > 50,000/mm3, (b) CNS or testicular disease at diagnosis, (c) T cell ALL and (d) specific abnormal chromosome. Protocol NHL-04-06 was used for patients with Burkitt's leukemia (L3 morphology). Figure 1 presents the medication used for each protocol and the respective cumulative dosage. Previous ALL survival between 2003 and 2005 from the Thai Pediatric Oncology Group for the 12 centers was used for outcome comparisons (Wiangnon et al., 2011).

Factors that impact on treatment outcome

In order to elucidate the factors that may affect the outcome of ALL treatment in our study, we developed a scoring system to classify all participating hospitals in terms of supportive care and available laboratory investigations. Grading of supportive care was based on: (a) promptness in administering appropriate antibiotic and antifungal agents; (b) use of granulocyte colony stimulating factor (G-CSF); and, (c) the time required to prepare pack red cells and platelet concentrate for transfusion support. Grading for hospital laboratory investigations was based on the availability of immuno-phenotype and chromosome cytogenetic studies. The patient's family socioeconomic grade was based on monthly income and the number of family members. Treatment compliance was based on regularity of follow-up and frequency of abandonment of chemotherapy. Details of hospital classification and patient characteristics are presented in Table 1.

Statistical methods

Patients and disease characteristics were demonstrated using descriptive statistics. Overall survival (OS) was defined as the time from diagnosis to death. Event-free survival (EFS) was defined as time from diagnosis to event. Events were defined either as relapse or death. The Kaplan-Meier method was used to calculate survival curves and statistical significance of differences were determined using the log-rank test.

Results

Patient characteristic and treatment

We enrolled 486 children with ALL. Boys were more common than girls (1.4:1). The mean age was 5.64 years. The median initial white blood cell count (WBC) was 12,800/mm3. A respective 19 and 5 cases had CNS and testicular involvement at diagnosis. Four cases were diagnosed as having Down syndrome. A respective 63.6% (n=51), 10.5% (n=51), 1.8% (n=9) and 24.1%

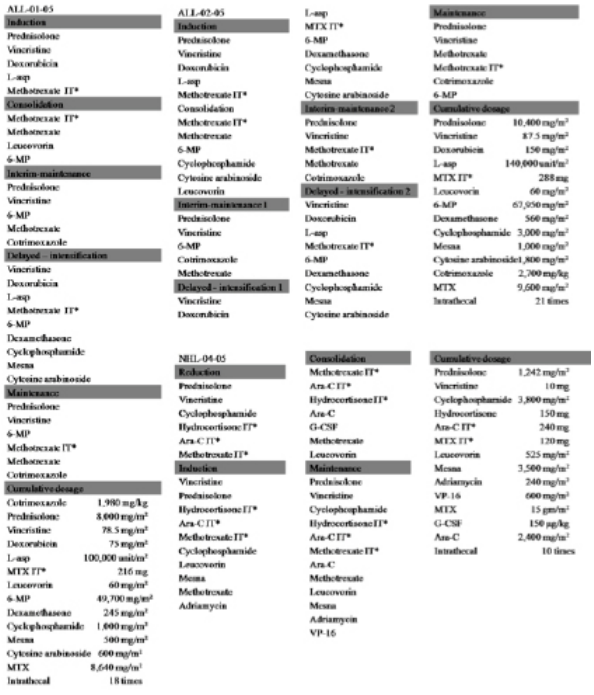

Figure 1. Medication Used for Each Protocol and Cumulative Dosage. *IT, intrathecal injection; Abbreviation: 6MP, 6-mercaptopurine; Ara-C, cytosine arabinoside; G-CSF, granulocyte colony stimulating factor; L-asp, L-asparaginase; MTX, methotrexate; VP-16, etoposide

Table 1. Questionnaire contents

For participating hospital	For patients and families
1. Supportive care	1. Socioeconomics of patient
1) Antibiotic choice in febrile neutropenia	1) Family income
2) Antifungal treatment in prolonged fever	2) Number of family members
3) Time required to get packed red cells and platelet transfusion	
4) G-CSF support	
2. Laboratory facilities	2. Compliance
1) Immuno-phenotype availability	1) Regularity of follow up
2) Chromosome availability	2) Regularity of drug taking

(n=117) immunophenotypes were classified as pre-B lineage, T-cell lineage, Burkitt's cell and non-specified lymphoid leukemia. Fifty percent (n=244) were treated with standard risk protocol (ALL-01-05), 48% (n=234) with high risk ALL protocol (ALL-02-05), and 1.6% (n=8) with Burkitt's cell protocol (NHL-04-06). Cases were from Bangkok (n=195), the northeast (n=175), the south (n=60) and the north (n=56). Of the Bangkok cases 118 of 195 were treated at Bangkok medical schools, while 137 of 291 upcountry cases were treated at provincial medical schools.

A respective 2, 7 and 3 hospitals were classified as having good, fair and minimal supportive care, while 8 and 4 had good and fair laboratory investigations. Accordingly, 42, 230 and 213 patients received good, fair and minimal supportive hospital care while 201 and 284 had good and fair laboratory-facility hospitals, respectively.

A respective 56, 169 and 131 cases were of good, fair and poor socioeconomic status while 373 and 28 demonstrated good and intermediate compliance.

Results of treatment

Most (91.8%) of ALL patients achieved complete remission after induction. The respective remission rates were 95.1%, 87.2% and 100% for the ALL-01-05 (standard risk), ALL-02-05 (high risk) and NHL-04-05 (Burkitt's cell leukemia) protocol. The death rates before completed remission were higher for high risk ALL compared to standard risk ALL (7.3% *vs* 1.6%). Of the 20.2% of ALL patients who relapsed, 17.1% were standard risk, 22.7% high risk and 37.5% Burkitt's cell leukemia. Relapses of ALL patients were mostly in bone marrow (7.7% in standard risk, 13.5% in high risk and 25% in Burkitt's cell leukemia) while CNS relapses were 6.5% and 5.1% in standard risk and high risk ALL, respectively (Table 2).

According to risk stratification, based on age and initial WBC count, the worst outcome was for patients with a WBC > 100,000/mm^3 (Table 3).

The overall survival of ALL treated by these Thai national protocols was 67.2%, which represents a non-statistically significant improvement from the previous 63.7% from the same institutions (p-value=0.06 Figure 2). Event-free survival of ALL patients in this study was 58.7%, which when classified by treatment protocols is 66.5%, 51.2% and 37.5% for standard risk, high risk and Burkitt's ALL, respectively. This represents a statistically significant difference in outcomes between the 3 risk groups (p-value <0.01, Figure 3). When the patients were classified according to hospital group, the respective event-free survival rate was 70.0%, 53.4%, 69.6% and 49.5% for medical schools in Bangkok, hospitals in Bangkok, provincial medical schools and provincial hospitals (p-value <0.01, Figure 4). The outcome for patients treated in Bangkok was better than those treated upcountry (69.9% *vs* 51.2%, p-value<0.01) (Figure 5).

Since there were differences in event-free survival between patients treated in Bangkok *vs* upcountry despite using the same protocol, we tested the factor(s) that might have an impact on these differences, whether related to patient socioeconomics, treatment compliance or hospital

Table 2. Results of Treatment

Result of ALL treatment	ALL 01-05	ALL 02-05	NHL 04-05
Death before complete induction	4 (1.6%)	17 (7.3%)	-
Complete remission	234 (95.1%)	204 (87.2%)	8 (100%)
No remission	5 (2%)	11 (4.7%)	-
Not assessable	3 (1.2%)	2 (0.9%)	-
Relapse	42 (17.1%)	53 (22.7%)	3 (37.5%)
Bone marrow (BM)	19 (7.7%)	31 (13.3%)	2 (25%)
Central nervous sysytem (CNS)	16 (6.5%)	12 (5.1%)	-
Testis	-	1 (0.4%)	-
BM + CNS	6 (2.4%)	9 (3.9%)	1 (12.5%)
BM + Testis	1 (0.4%)	-	-

Table 3. Outcome of ALL by Age and Initial white Blood Cell Count

Age group (year)	Event free survival	p-value
<1	58.69	
1 to 10	56.89	0.59
>10	54.35	
Initial WBC (/mm^3)	**Event free survival**	**p-value**
<10,000	58.31	
10,000-50,000	60.28	
50,000-100,000	60.88	
>100,000	44.12	<0.01

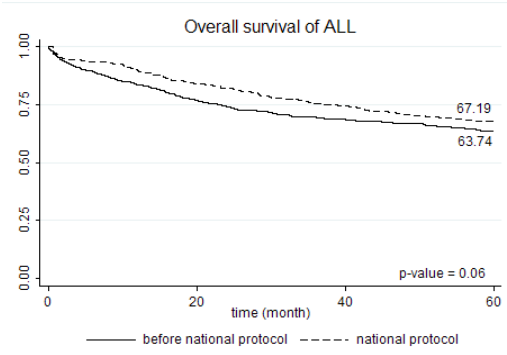

Figure 2. Survival in Children with Acute Lymphoblastic Leukemia, 2006-2008

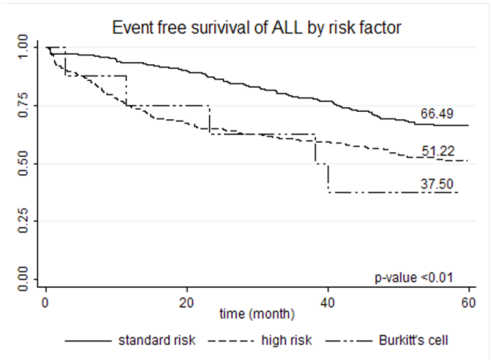

Figure 3. Survival in Children with Acute Lymphoblastic Leukemia by Risk

supportive care, or laboratory investigations. There were in fact significant differences (p-value=0.02) in event-free survival among the different socioeconomic groups (i.e., 65.5%, 61.1% and 47.5% for good, fair and poor, respectively). Event-free survival according to patient compliance was significantly better for good compared to intermediate compliance (59.4% *vs* 42.9%, p-value=0.02). Event-free survival of patients according to hospital supportive care was not significantly different (60.0% *vs* 57.5% *vs* 59.8%, p-value=0.59). Similarly, event-free survival of patients according to laboratory availability in hospital was also not significantly different (59.9% *vs* 56.8%, p-value=0.27)(Figure 6).

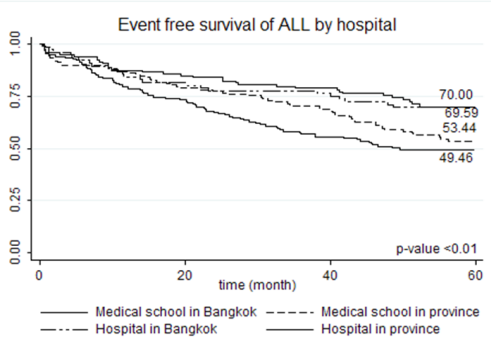

Figure 4. Survival in Children with Acute Lymphoblastic Leukemia by Treating Hospital

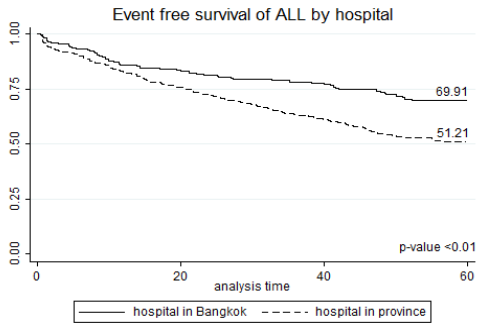

Figure 5. Survival in Children with Acute Lymphoblastic Leukemia by Treating Hospital in Bangkok and Provinces

Discussion

The global range in survival for ALL in children varies from < 60% to ≥ 90% in developed countries while survival in Thailand between 1995-2009 ranges between 51% and 59% (Allemani, 2015). In 2006, the Thai Pediatric Oncology Group (ThaiPOG) developed the national guidelines for treatment of childhood leukemia in order to meet the international standard and implement a practicable treatment policy for the country as a whole. Survival subsequently improved in patients in the standard risk group but not in the high risk group (Seksarn, 2011; Wiangnon, 2011). The survival of children with ALL in Khon Kaen (in the northeastern region) between 1985 and 2009 had already been rising, but did especially so after implementation of the national protocol in 2006 (Wiangnon, 2014). In the current study, the overall survival of ALL treated using the Thai national protocols trended to improve (i.e., from the previous 63.7% to 67.2%), albeit the difference was not statistically significant. It is, therefore, not certain whether nationwide implementation of standard protocols would be beneficial. This outcome is, moreover, still less than that in developed countries (Smith, 1999; Viana et al., 2001, Gutta et al., 2005; Allemani et al., 2015) despite our (a) stratifying patients according to risk factors (viz., age, white blood cells and immunophenotype) and (b) treating Burkitt's ALL with a distinct protocol. This stratification, however, might not represent the true risk as defined in other studies, since a molecular study was not included in our current study. Some patients, who were defined as low risk, might actually have been intermediate or high risk. As such, according to the risk stratification by the Thai national protocol, the ratio of risk stratification of high risk to low risk was notably higher than that observed in several studies (Gu et al., 2008; Hazar et al., 2010, Mukda, 2011).

Since the treatment expenses for over 90% of the

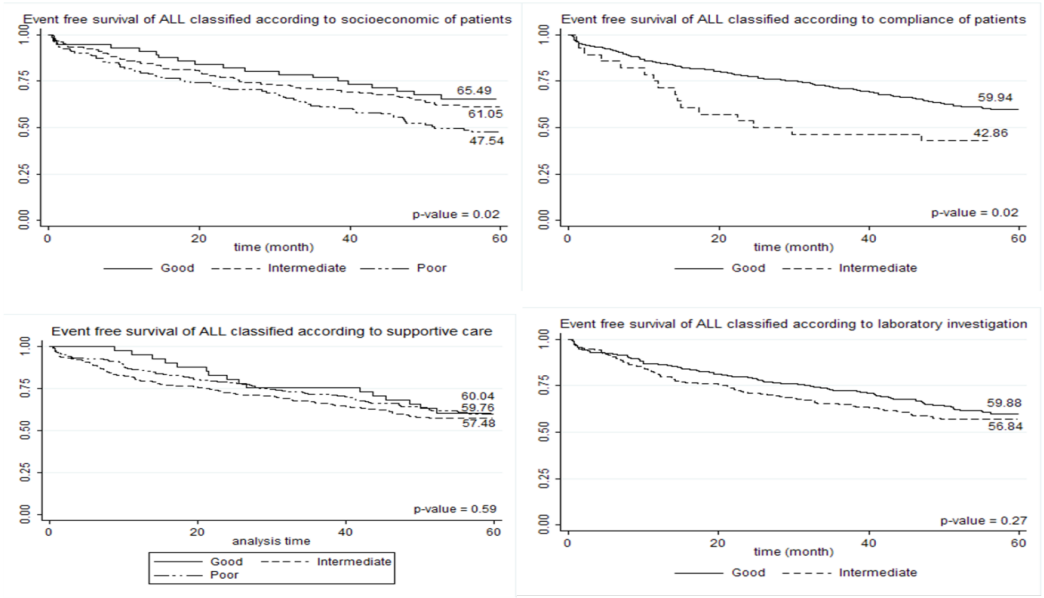

Figure 6. Survival in Children with Acute Lymphoblastic Leukemia by Socioeconomic Status, Treatment Compliance, Supportive care and Laboratory Facility of Treating Hospital

studied patients were reimbursed by the Thai universal health coverage system (Tangcharoensathien, 2010), all socio-economic classes had access to treatment in a nearby hospital. This means that treatment accessibility was not limiting outcomes. The factor that was associated with poorer outcomes in this study was an initial white blood cell count (WBC) over 100,000/mm^3. Notwithstanding, Tharnprisarn showed that a relapse-rate in childhood ALL, treated under the Thai national protocol, was significantly associated with age under 1 year; not the initial WBC (Tharnprisarn, 2014). A more appropriate approach is, therefore, needed to control this group of ALL.

The reason why there is no significant improvement in outcome may be due to multiple interacting factors, including: (a) the lack of any significant difference in protocols between the two eras in most hospitals; (b) the supportive care facilities in some institutions may not be adequate to cope with complications (Tharnprisarn, 2014); (c) poor socioeconomics (Gupta et al., 2014; Tharnprisarn, 2014); and/or, (d) poor treatment compliance (Oliveira et al., 2011; Gupta et al., 2014; de Tharnprisarn, 2014).

Our study showed that there were significant differences in the outcome of ALL treated in Bangkok compared to provincial hospitals. We tried to elucidate the reasons behind this discrepancy by grading hospitals (based on supportive care and laboratory facilities) and grading patients (based on socioeconomics and treatment compliance). Although we found no differences in outcomes based on different grades of supportive care or laboratory facilities, significant differences were found in outcomes of patients with poorer socioeconomics and compliance. Our findings agree with previous studies in which socioeconomic status was a major influence on treatment outcome (Mostert et al., 2011). Patient compliance—both adherence to oral chemotherapy and regular attendance to follow up clinics—is also considered a major influence (Bhatia et al., 2012). Non-compliance is hypothesized to be one of the mechanisms that underlie the adverse influence of low socioeconomic on ALL outcome (de Oliveira et al., 2004). Patients with a low socioeconomic status trend to experience greater difficulty attending scheduled clinics and adhering to prescribed medication(s) (Prichard et al., 2006). Other factors related to abandonment of treatment include disbelief in the possibility of a cure and distress caused by side-effects (Gupta et al., 2013).

The best way to achieve a better outcome for childhood ALL treatment is to improve compliance to treatment through an effective comprehensive program that includes: (a) parental education; (b) family affective management; (c) a patient tracking system; and, (d) social services for families (i.e., transportation, food and lodging subsidies) (Prichard et al., 2006; Gupta et al., 2013). To meet international standards and improve treatment outcomes, the ThaiPOG has revised the protocol for treatment of acute leukemia in 2013 and implemented the practicable treatment policy for the whole country (Thai Pediatric Oncology Group, 2014).

In conclusion, the outcome of childhood leukemia in Thailand remains inferior to rates in developed countries. Implementation of the Thai national protocol did not significantly improve the survival rate of ALL. Strict adherence to treatment protocols and financial support for families with a low socioeconomic status should be the primary emphases for improving treatment outcomes..

Acknowledgements

The authors are grateful for grant support from the Clinical Research Collaboration Network (CRCN) and Office of National Research Council of Thailand (NRCT). The authors thank (a) Ms Sommaphan Tabjareon for her keen data management (b) the staff of the ThaiPOG for their contribution and assistance in data collection (Nittaya Visanuyothin, MD. (Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima); Pattra Thanarattanakorn, MD. (Faculty of Medicine at Chiang Mai Hospital, Chiang Mai University, Chiang Mai); Yujinda Lektakul, MD. (Supprasithiprasong Hospital, Ubon Ratchathani); Somporn Wangruangsathit, MD. (Buddhachinaraj Hospital, Phitsanulok); Rachata Lumkul, MD. (Hematology-Oncology Division, Department of Pediatrics, Phramongkutklao Hospital); Samart Pakakasama, MD. (Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University) and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation.

References

Allemani C, Weir HK, Carreira H, et al (2015). Global surveillance of cancer survival 1995-2009: analysis of individual data for 25676887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*, **385**, 977-1010.

Bhatia S, Landier W, Shangguan M, et al (2012). Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. *J Clin Oncol*, **30**, 2094-101.

de Oliveira BM, Valadares MT, Silva MR, et al (2011). Compliance with a protocol for acute lymphoblastic leukemia in childhood. *Rev Bras Hematol Hemoter*, **33**, 185-9.

de Oliveira BM, Viana MB, Zani CL, et al (2004). Clinical and laboratory evaluation of compliance in acute lymphoblastic leukemia. *Arch Dis Child*, **89**, 785-8.

Gupta S, Wilejto M, Pole JD, et al (2014). Low socioeconomic status is associated with worse survival in children with cancer: a systematic review. *PLOS ONE*, **9**, 89482.

Gupta S, Yeh S, Martiniuk A, et al (2013). The magnitude and predictors of abandonment of therapy in paediatric acute leukaemia in middle-income countries: a systematic review and meta-analysis. *Eur J Cancer*, **49**, 2555-64.

Gutta G, Capocaccia R, Stiller C, et al (2005). Childhood cancer survival trends in Europe: A EUROCARE working group study. *J Clin Oncol*, **23**, 3742-51.

Gu LJ, Li J, Xue HL, et al (2008). Clinical outcome of children with newly diagnosed acute lymphoblastic leukemia treated in a single center in Shanghai, China. *Leuk Lymphoma*, **49**, 488-94.

Hazar V, Karasu GT, Uygun V, et al (2010). Childhood lymphoblastic leukemia in Turkey: factors influencing treatment and outcome: a single center experience. *J Pedaitr Heamtol Oncol*, **32**, 317-22.

Hunger SP, Lu X, Devidas M, Camitta BM, et al (2012). Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol*, **30**, 1663-9.

Mostert S, Sitaresmi MN, Gundy CM, et al (2006). Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. Pediatrics, **118**, 1600-6.

Mukda E, Pintaraks K, Komvilaisak P, et al (2011). Cytochemistry and multi-color flow cytometric immunophenotype for diagnosis of childhood acute leukemia. *J Hematol Transfus Med*, **21**, 23-31.

Pritchard M, Butow P, Stevens M, et al (2006). Understanding medication adherence in pediatric acute lymphoblastic leukemia: a review. *J Pediatr Hematol Oncol*, **28**, 816-23.

Seksarn P (2011). Outcome of childhood leukemia, ThaiPOG study. St Jude-VIVA forum in pediatric oncology, Singapore.

Smith MA, Ries LAG, Gurney JG, Ross JA (1999). Retinoblastoma. In: Ries LAG, Smith MA, Gurney JG, Tamra T. Young JL, Bunin GR, editors. Cancer incidence and survival among children and adolescents: Unites States SEER Program 1975-1995. NIH Pub. No. 99-4649; 73-8.

Stanulla M, Schrappe M. (2009). Treatment of childhood acute lymphoblastic leukemia. *Semin Hematol*, **46**, 52-63.

Tangcharoensathien V, Swasdiworn W, Jongudomsuk P, et al (2010). Universal coverage scheme in Thailand: equity outcomes and future agendas to meet challenges. Background paper, 43; World health report, World Health Organization.

Thai Pediatric Oncology Group (2014). National Protocol for treatment of childhood cancer 2014. Bangkok, M Print Corporation.

Tharnprisan P, Khiewyoo J, Sripraya P, Wiangnon S (2013). Relapse-free rate with childhood acute lymphoblastic leukemia treated under the Thai national protocol. *Asian Pac J Cancer Prev*, **14**, 1127-30.

Viana MB, Fernandes RA, de Oliveira BM, et al (2001). Nutritional and socio-economic status in the prognosis of childhood acute lymphoblastic leukemia. *Haematologica*, **86**, 113-20.

Wiangnon S, Jetsrisuparb A, Komvilaisak P, Suwanrungruang K (2014). Childhood cancer incidence and survival 1985-2009, Khon Kaen, Thailand. *Asian Pac J Cancer Prev*, **15**, 7989-93.

Wiangnon S, Veerakul G, Nuchprayoon I, et al (2011). Childhood cancer incidence and survival 2003-2005, Thailand: study from the Thai pediatric oncology Group. *Asian Pac J Cancer Prev*, **12**, 2215-20.