Outcome of Acute Lymphoblastic Leukemia Treatment Using National Protocols at the Queen Sirikit National Institute of Child Health

Somjai Kanjanapongkul MD*

** Hemato/Oncology Unit, Queen Sirikit National Institute of Child Health, College of Medicine, Rangsit University, Bangkok, Thailand*

Objective: *To evaluate the outcome of acute lymphoblastic leukemia (ALL) treatment at the Queen Sirikit National Institute of Child Health (QSNICH) after using national protocols.*

Material and Method: *Seventy-six pediatric patients with newly diagnosed with ALL, who were treated in Queen Sirikit National Institute of Child Health using the national protocols during March 2006 and February 2008, were enrolled. The national protocols were sub-classified by clinical risk factors and morphology of leukemic cells of the patients at initial presentation into 3 groups as standard risk (ALL-01-05), high-risk (ALL-02-05), and mature B-ALL or L3 (NHL-04-06) protocol. Overall survival (OS) and event-free survival (EFS) were determined by using Kaplan-Meier survival curves.*

Results: *The overall survival rate of ALL patients treated using the national protocols was 83.85% (88.06% in standard group, 82.01% in high-risk group, and 75% in L3 protocol). The mortality rate and event-free survival of ALL patients was 13.33% and 72.50%, respectively.*

Conclusion: *The national protocols for ALL showed benefit in the improvement of outcomes from treatment in childhood ALL.*

Keywords: *Childhood ALL, National protocols, Outcome*

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Acute leukemia had been reported by Thai Pediatric Oncology Group (Thai-POG) to be the most common malignancy in Thai children, occurring in 52.3% of patients[1]. The report also scaled that while the 5-year, overall survival of acute leukemia in Thailand was 57.56%, that of ALL was 64.9%, which was much lower than that in developed countries. The overall survival rates were also different in each regional cancer center because of variety in treatment protocols. In 2005, Thai-POG developed standard national protocols for childhood leukemia treatment to improve the outcome in these children. These protocols have been widely implemented in multi-cancer centers throughout the country. Newly diagnosed patients with ALL have been treated with three different treatment protocols depending on clinical risks and blast cell morphology at initial diagnosis. This is a report of the outcome of treatment of ALL patients using the Thai POG protocol since its implementation at QSNICH since 2006.

Correspondence to:
Kanjanapongkul S, Hemato/Oncology Unit, Queen Sirikit National Institute of Child Health, College of Medicine, Rangsit University, Bangkok 10400, Thailand.
Phone & Fax: 0-2354-8439
E-mail: ksomjaik@gmail.com

Material and Method

Seventy-six newly diagnosed ALL patients, younger than 15 years of age, who were enrolled using the national protocols since 2006, were included in this report. The leukemic patients were stratified into three different treatment protocol groups based on the criteria shown in Table 1. Details of chemotherapeutic agents in each protocol are shown in Fig. 1.

Statistical analysis

Demographic data were summarized by descriptive statistic. Event-free survival (EFS) and overall survival (OS) were estimated using the method of Kaplan-Meier, and statistically significant differences were determined by log-rank test. Overall survival (OS) was defined as the time from diagnosis to death. Event-free survival (EFS) was defined as time from diagnosis to events. Events were defined as relapse or death.

Results

There were 76 patients with newly diagnosed ALL during March 2006 to February 2008. There were

Table 1. Criteria to sub-classified clinical risk group at initial diagnosis

ALL-01-05 (standard risk ALL)	ALL-02-05 (high risk ALL)	NHL-04-06 (mature B/L3-ALL)
Initial WBC <50,000/mm^3 Age between 1-10 year	Initial WBC >50,000/mm^3 Age <1 year; >10 year CNS disease at diagnosis Testicular involvement at diagnosis T-cell characteristic Specific abnormal chromosome	L3-ALL morphology

ALL-01-05
Induction
Prednisolone
Vincristine
Doxorubicin
L-as
Methotrexate IT*
Consolidation
Methotrexate IT*
Methotrexate
Leucovorin
6-MP
Interim-maintenance
Prednisolone
Vincristine
6-MP
Methotrexate
Cotrimoxazole
Delayed - intensification
Vincristine
Doxorubicin
L-as
Methotrexate IT*
6-MP
Dexamethasone
Cyclophosphamide
Mesna
Cytosine arabinoside
Maintenance
Prednisolone
Vincristine
6-MP
Methotrexate IT*
Methotrexate
Cotrimoxazole
Cumulative dosage
Cotrimoxazole 1,980 mg/kg
Prednisolone 8,000 mg/m^2
Vincristine 78.5 mg/m^2
Doxorubicin 75 mg/m^2
L-as 100,000 unit/m^2
MTX IT* 216 mg
Leucovorin 60 mg/m^2
6-MP 49,700 mg/m^2
Dexamethasone 245 mg/m^2
Cyclophosphamide 1,000 mg/m^2
Mesna 500 mg/m^2
Cytosine arabinoside 600 mg/m^2
MTX 8,640 mg/m^2
Intrathecal 18 times

ALL-02-05	L-as	**Maintenance**
Induction	MTX IT*	Prednisolone
Prednisolone	6-MP	Vincristine
Vincristine	Dexamethasone	Methotrexate
Doxorubicin	Cyclophosphamide	Methotrexate IT*
L-as	Mesna	Cotrimoxazole
Methotrexate IT*	Cytosine arabinoside	6-MP
Consolidation	**Interim-maintenance 2**	**Cumulative dosage**
Methotrexate IT*	Prednisolone	Prednisolone 10,400 mg/m^2
Methotrexate	Vincristine	Vincristine87.5 mg/m^2
6-MP	Methotrexate IT*	Doxorubicin 150 mg/m^2
Cyclophosphamide	Methotrexate 6-MP	L-as140,000 unit/m^2
Cytosine arabinoside	Cotrimoxazole	MTX IT*288 mg
Leucovorin	**Delayed - intensification 2**	Leucovorin60 mg/m^2
Interim-maintenance 1	Vincristine	6-MP67,950 mg/m^2
Prednisolone	Doxorubicin	Dexamethasone 560 mg/m^2
Vincristine	L-as	Cyclophosphamide 3,000 mg/m^2
6-MP	Methotrexate IT*	Mesna1,000 mg/m^2
Cotrimoxazole	6-MP	Cytosine arabinoside 1,800 mg/m^2
Methotrexate	Dexamethasone	Cotrimoxazole 2,700 mg/kg
Delayed - intensification 1	Cyclophosphamide	MTX9,600 mg/m^2
Vincristine	Mesna	Intrathecal21 times
Doxorubicin	Cytosine arabinoside	

NHL-04-05	**Consolidation**	**Cumulative dosage**
Reduction	Methotrexate IT*	Prednisolone 1,242 mg/m^2
Prednisolone	Ara-C IT*	Vincristine10 mg
Vincristine	Hydrocortisone IT*	Cyclophosphamide 3,800 mg/m^2
Cyclophosphamide	Ara-C	Hydrocortisone 150 mg
Hydrocortisone IT*	G-CSF	Ara-C IT*240 mg
Ara-C IT*	Methotrexate	MTX IT*120 mg
Methotrexate IT*	Leucovorin	Leucovorin525 mg/m^2
Induction	**Maintenance**	Mesna3,500 mg/m^2
Vincristine	Prednisolone	Adriamycin240 mg/m^2
Prednisolone	Vincristine	VP-16600 mg/m^2
Hydrocortisone IT*	Cyclophosphamide	MTX15 gm/m^2
Ara-C IT*	Hydrocortisone IT*	G-CSF150 µg/kg
Methotrexate IT*	Ara-C IT*	Ara-C2,400 mg/m^2
Cyclophosphamide	Methotrexate IT*	Intrathecal10 times
Leucovorin	Ara-C	
Mesna	Methotrexate	
Methotrexate	Leucovorin	
Adriamycin	Mesna	
	Adriamycin	
	VP-16	

*Standard-risk (SR) ALL and L3 protocol treated patients did not receive cranial irradiation, whereas high-risk (HR) patients received prophylactic cranial irradiation.

Fig. 1 Details of the chemotherapeutic agents in protocols.

41 boys (53.95%) and 35 girls (46.05%). The demographic data about age and initial white blood count (WBC) among the treatment groups were described in Table 2. The outcome of ALL treatment such as OS was 83.85%, 88.6% in standard risk (SR) group, 82.01% in high-risk (HR) group, and 75% in L3 group, as showed in Fig. 2, 3.

The mortality and relapse rates were 13.33% (n = 10) and 21.05% (n = 16) respectively. Bone marrow was the most common site of relapse, occurring 13.16%

Table 2. Demographic data by age and initial WBC among the treatment groups

	Standard risk-ALL (n = 35)	High risk-ALL (n = 37)	ALL-L3 (n = 4)
Age (year)			
Mean	3.16	7.91	4.58
Min	1.5	0.58	3.58
Max	7.41	13.16	5.67
Initial WBC/cc. mm.			
Mean	6,665	56,970	96,000
Min	1,660	800	5,300
Max	32,100	386,380	280,190

(SR4, HR5, L31), then CNS 7.89% (SR2, HR4) and testicular site 1.31% (HR1), respectively. The overall-EFS was 72.50% (95% CI 58.08-82.67) as showed in Fig. 4.

Discussion

The present study shows the OS rate at QSNICH after using national protocols to be 83.85%, this shows significant improvement when compared to a previously reported result of 59.6%[1]. The main difference in the national protocols from Thai-POG, when compared to the past treatments, is more intensive chemotherapy, such as high dose methotrexate in consolidation phase or a delayed intensification phase[2-5]. The intensive chemotherapy and classification of risk group treatment has helped to improve the outcome including OS and EFS of ALL patients, especially in high-risk patients. However, the event-free survival rate in standard risk group was disappointing compared to the reports from developed countries[6-11] because of the high incidence of disease relapse. In the upcoming national protocol from Thai-POG, the intensity of chemotherapy for standard risk groups would be adjusted.

Conclusion

Compared to the previous report, there was significant improvement in the OS and EFS of ALL treatment after implementation of national protocols at Queen Sirikit National Institute of Child Health. Even though the OS in the standard risk group was highest, the EFS was lowest among these three groups.

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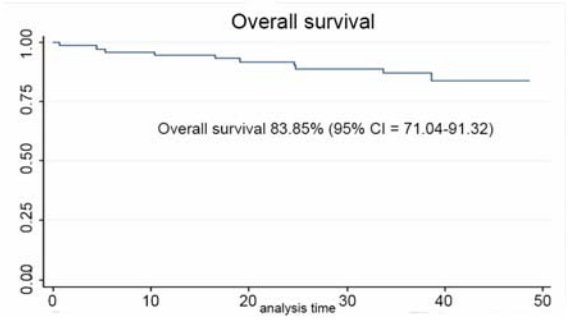

Fig. 2 Overall survival of ALL patients treated with national Thai-POG protocols.

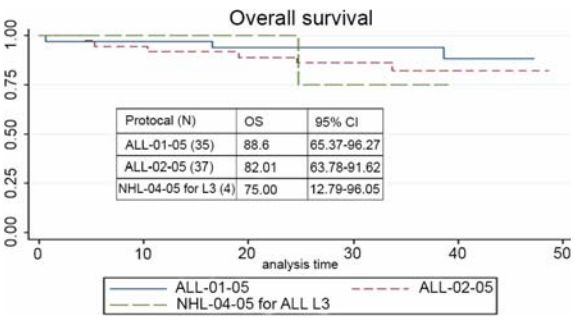

Fig. 3 Overall survival of ALL patients in different treatment group.

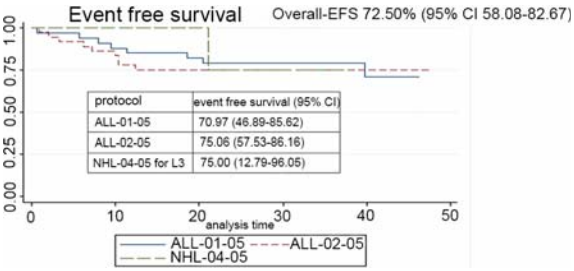

Fig. 4 Event free survival of ALL patients in different treatment group.

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Potential conflicts of interest

None.

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ผลการรักษาผู้ป่วยเด็กโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมโฟบลาสต์โดยใช้ National Protocols ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

สมใจ กาญจนาพงศ์กุล

วัตถุประสงค์: *เพื่อประเมินผลการรักษาผู้ป่วยใหม่โรคมะเร็งเด็กชนิดลิมโฟบลาสต์ในสถาบันสุขภาพเด็กฯ หลังปรับใช้แผนการรักษาตาม national protocols*

วัสดุและวิธีการ: *ผู้ป่วยใหม่จำนวน 76 ราย ได้รับการวินิจฉัยมะเร็งเม็ดเลือดขาวชนิดลิมโฟบลาสต์ระหว่าง เดือนมีนาคม พ.ศ. 2549 ถึง เดือนกุมภาพันธ์ พ.ศ. 2551 ที่ได้รับการรักษาตามแผน national protocols โดยแบ่งกลุ่มการรักษาตามความเสี่ยงทางคลินิกและลักษณะเซลล์มะเร็งเม็ดเลือดขาวของผู้ป่วยตั้งแต่แรกการวินิจฉัยเป็น 3 กลุ่ม ได้แก่ กลุ่มความเสี่ยงปกติ (ใช้ ALL-01-05) กลุ่มความเสี่ยงสูง (ใช้ ALL-02-05) และกลุ่ม L3 (ใช้ NHL-04-06) ประเมินผลการรักษาโดยดูอัตราการรอดชีพและอัตราการปลอดโรคด้วยวิธี Kaplan-Meier survival curves*

ผลการรักษา: *อัตราการรอดชีพในผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดลิมโฟบลาสต์ที่ได้รับการรักษาตามแผนการรักษา national protocols โดยรวมที่ร้อยละ 83.85 เมื่อแยกตามกลุ่มความเสี่ยงปกติร้อยละ 88.06 กลุ่มเสี่ยงสูงร้อยละ 82.01 และร้อยละ 75 ในผู้ป่วยกลุ่ม L3 สำหรับอัตราตายและอัตราปลอดโรคอยู่ที่ร้อยละ 13.33 และ 72.5 ตามลำดับ*

สรุป: *พบอัตราการรอดชีพสูงขึ้นในผู้ป่วยทุกกลุ่มที่ได้รับการรักษาตามแผนการรักษา national protocols*