THE RESULT OF CCG 1961 PROTOCOL TREATMENT WITH HIGH RISK ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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ABSTRACT:

Background: *Acute lymphoblastic leukemia (ALL) remains the most common malignancy in children. It accounts approximately 75% of all cases of childhood leukemia. High risk ALL in children can be cured with intensive protocol. The aim of this study was to evaluate the result of the modified CCG- 1961 protocol treatment of high risk ALL in children at National Children's Hospital (NCH).*

Methods: *Prospective study 102 patients from 6/2008 to 12/2012. The patients of high risk ALL was confirmed and were treated according to the modified CCG 1961 protocol. Statistical analysis was performed with the SPSS program.*

Results: *88.24% achieved initial complete remission. According to Kaplan Meyer 5 years: 5- year overall survival (OS) is 48.6% ± 5.0; 5- year event free survival (EFS): 46% ± 5.0. Treatment of boys was better than of girls: OS and EFS were 54.8% and 52.9% compare with 30.5% and 29.6% respectively (p< 0,05). Rapid early response (RER) group had OS and EFS higher than slow early response (SER): 49.6% and 47.8% vs. 31.5% and 30.4%.*

Conclusion: *Overall survival and event free survival was 48.6% and 46%. Relapse rate was 16.7%. Mortality rate was 37.25%.*

Key words: *Acute lymphoblastic leukemia, ALL, Overall survival OS, EFS.*

I. BACKGROUND

Leukemia is one of the most common types of cancer among children around the world. Acute lymphoblastic leukemia (ALL) accounts for approximately 75% of all cases of childhood leukemia. In recent years, pediatric ALL is often citedas one of the true success stories of modern medicine, with the cure rate improving from zero prior to the advent of modern chemotherapy and radiation therapy to current overall event- free survival (EFS) rate of about 80%. This success has been due to the development of classifications, active chemotherapeutic agents, immunology, genetics and bio-molecules into diagnosis, treatment, monitoring the disease and understanding the prognosis factors. So far, no research on high-risk childhood ALL with complete assessment and proper clinical protocol applicable to Vietnam has been conducted. Thus, we carried out our research on the topic ***"The result of protocol CCG 1961 using modified with high-risk ALL in children at National Children's Hospital".***

II. PATIENTS AND METHODOLOGY

2.1. Patients

The target patients for research are 102 high- risk ALL patients admitted to Department of Oncology

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of NCH between the period from 1/6/2008 to 31/12/2012. Patients are treated and monitored according to modified CCG 1961 protocol. The time of observation is until 31/5/2015.

The protocol being used for treatment is the US CCG 1961 arm B. This is a protocol for high-risk ALL patients, with some modifications for better application in Vietnam context such as: L-Asparaginase(ASP) is a form of E. Coli ASP from Kyowa (Japan), 6 thioguanin is replaced by 6MP; intrathecal by cyratabine day 0 is replaced by MTX. These replacements don't affect to the outcome because we can use E. Coli ASP or PEG ASP as protocol, 6MP and 6TG is similar in anti-metabolismer group.

2.2. Methodology

Prospective study and follow up the results of high-risk ALL patients according to modified CCG 1961 protocol. Statistical analysis was performed with the SPSS program.

III. RESULTS

There are 102 patients who are treated according to CCG 1961 protocol. The patients are followed up from the start of treatment until death or until the end of treatment and regular check-up afterwards. Male/ Female ratio is 1.7.

3.1. Induction phase results: Among 102 patients treated according to the CCG 1961 protocol, 3 died before day 7 of the induction phase, 99 others undergo bone marrow aspiration to examine the responsiveness to the treatment. Results are as follow:

Table 3.1. Bone marrow on day 7 of induction phase

On day 7	n	%
M1	75	75.8
M2	8	8.1
M3	16	16.1
Total	99	100

Comments: Percentage of patients who reach RER (Rapid early response) is 82.9% (75.8% M1 and 8.1% M2), only 16.1% have SER (Slow early response: M3).

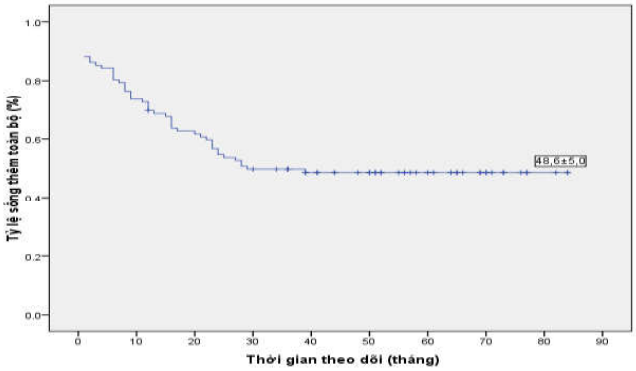
Table 3.2. Results of induction phase

Results	n	%
Complete remission	90	88.24%
Fatality	12	11.76%
Total	102	100%

Comments: 88.24% of patients reach complete remission by the end of induction phase. 12 patients (11.76%) died during treatment.

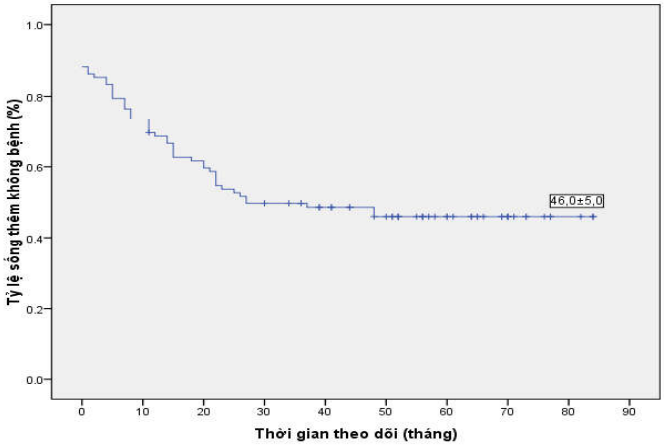
3.2. CCG 1961 protocol results based on Kaplan-Meyer

90 patients continue post- induction and follow up (77 RER and 13 SER). Results show that 17 suffer from relapse (16.67%) and 26/90 patients died post- induction.



Graph 3.1. OS ratio based on Kaplan-Meier

Comment: Percentage of overall survical (OS) patients for 5 years is 48.6 ± 5.0%.



Graph 3.2. EFS ratio based on Kaplan-Meier.

Comment: Even Free survival (EFS) ratio for 5 years is 46.0 ± 5.0%.

Table 3.3. OS and EFS by gender

Gender	**5 years OS**			**5 years EFS**		
	%	SD	95% CI	%	SD	95% CI
Boys	54.8	4.6	45.8 – 63.7	52.9	4.6	43.9 – 61.9
Girls	30.5	4.5	21.7 – 39.4	29.6	4.6	20.6 – 38.6
	p = 0.006			p = 0.01		

Comments: Boys have higher OS ratio than girls, 54.8% ± 4.6% and 30.5% ± 4.5% respectively. EFS ratio of boys is also higher than that of girls (52.9 ± 4.6% and 29.6 ± 4.6%). Statistical significance p < 0.05.

Table 3.4 OS and EFS by age group

Age	**5 years OS**			**5 years EFS**		
	%	SD	95% CI	%	SD	95% CI
< 10	46.8	6.2	34.7 – 59.0	45.1	4.5	36.3 – 54.0
≥ 10	47.1	4.5	38.3 – 55.9	46.1	6.3	33.7 – 58.5
	p = 0.97			p = 0.905		

Comments: OS and EFS for children aged above and below 10 is 47.1±4.5% and 46.8±6.2%, 45.1±4.5% and 46.1±6.3% respectively. There is no difference between the two age groups (p>0.05).

Table 3.5. OS and EFS by bone marrow response on day 7

Day 7 response	**OS by day 7 response**			**EFS by day 7 response**		
	%	SD	95% CI	%	SD	95% CI
RER	49.6	3.9	41.9 – 57.3	47.8	3.9	40.1 – 55.6
SER	31.1	8.1	15.1 – 39.8	30.4	8.3	14.2 – 46.6
	p = 0.069			p = 0.09		

Comments: OS and EFS ratio of the RER on day 7 of induction phase are higher than that of the SER group (49.6% and 47%, 31.1% and 30.4%). However, this difference has no statistical significance (p>0.05).

IV. DISCUSSION

According to CCG 1961 protocol, bone marrow aspirate must be checked on day 7 of induction phase to assess the response to treatment. Our research indicates that RER percentage is 83.9% (75.8% M1 and 8.1% M2), SER (M3) is 16.1% (table 3.1). When compared this result with that of the CCG 1961 research group (RER is 71.4% & SER is 28.6%), our SER percentage is higher but the death ratio before day 7 is higher (3/102) than that of CCG 1961 research (3/2057). Arika M (Japan) from 1988-1999 on 116 patients, which assess on day 14 shows that: 69 children are M1 (59.5%), 25 patients are M2 (21.6%), 22 patients are M3 (18.9%). This result is similar to ours. Patients with M2 and M3 of day 7 will have their bone marrow aspirate on day 14. Results show that 8 M2 patients reach M1 on day 14 so they was continued arm B of protocol (RER), 16 M3 patients reach M1 on day 14, 3 reach M2, 3 patients died due to septisemia, coagulation disorsers before day 14 so only 13 patients was continued protocol (SER). As CCG 1961, we evaluated bone marrow day 28 and showed 100% complete remission (M1). Table 3.2 shows that complete remission after induction phase has 88.24%, death rate in this phase is 11.76%. Meanwhile, the American CCG 1961 research group has 21/2057 (1.02%). CV Ha (Hue) reported the ALL treatment death rate is 44% in the first 28 days of treatment. The reason for the high death rate is severe infection due to neutropenia and uncontrolled bleeding, brain hemorrhage. Comparing with other research groups in the world shows that death rate during induction phase is a serious problem that requires attention, supportive care such as proper & effective antibiotic usage and adequate supplement of blood products to prevent possible strokes has large impact on treatment results.

Relapse percentage is 16.67% (17 patients), among them 15 patients relapse while the treatment (2 patients relapse very early in less than 6 months, this may be explained by unfavorable factors) and 2 patients relapse late. Other groups with the same relapse results: Ma-Spore 17.9%; CCG 1961 16.92%; UKALL 97-99: 16%.

Graph 3.1 & 3.2 shows OS and EFS rates 5 years. Based on this estimation, our OS result is 48.6 ± 5.0% and EFS is 46 ± 5,0%. This is a humble result when compared to the result of CCG 1961 protocol published by Nita LS in 2007 with 80.4 ± 1.4% for OS and 71.3 ± 1,6% for EFS. Allen Yeoh (Singapore 2012) applied Ma-Spore protocol in 2003 give the results of 71.8% for OS rate 5 years and 50.6% for EFS rate 5 years. Veeman A (Holland) published the high-risk ALL treatment based on Dutch ALL-9 (1997-2004) results of 71% for OS rate and 78% for EFS rate (5 years). This shows that not only using the correct medicine based on the protocol but also the doctor must have enough experience in supportive care and side effect treatment well, isolation therapy and healthy nutrition also increase patients' survival rates. Patients' deaths in our research are mostly due to infection as a result of severe neutropenia decrease and uncontrolled bleeding. Comparing OS and EFS 5 years ratio between boys and girls in our research shows significant difference: boys have better ratio than girls, this difference is statistically significant when $p < 0.05$. Allen Yeoh published the treatment results based on Ma-Spore protocol in 2003 when comparing between 2 genders show no difference, EFS rates after 8 years are 80% in boys and 81.1% in girls. Chritensen MS shows that boys have worse prognosis factors than girls but did not die of infection, girls have higher death rates due to infection of 4.4% compared to 2.1% in boys. Allen Y research based on Ma-Spore protocol shows that there is a statistically significant difference between the EFS rate of 2 groups above and below 9 years old ($p=0.000$), survival rate for age group >9 is 73.4% while age group <9 is 83.8% after 8 years. Bauruchel A shows that survival rate for age group <10 is higher than that of age group >10 in research

by Dana Farber Cancer Institute (1991-2000), children aged below 10 (n=685) and children aged above 10 (n=108) shows EFS rates after 6.5 years is 85%±1% & 77%±4%. However, these results do not have statistical significance (p=0.09). Among 90 patients continued with CCG 1961 protocol there are 77 show RER and 13 show SER on day 7 of induction phase. Comparison in terms of OS and EFS rates between these 2 groups show that RER patients have higher survival rate than SER patients. However, this difference is not statistically significant (p>0.05), maybe because the number of SER patients is small when among 13 SER patients only 6 complete treatment.

V. CONCLUSION

Complete remission of induction phase is 88.2%. OS rate and EFS rate 5 years based on Kaplan-Meier estimation are 48.6% and 46% respectively; boys have higher survival rates than girls (54.8% and 52.9% compare to 30.5% and 29.6%) with statistical significance with p<0.05; the ratio of RER is higher than that of SER (49.6% & 47.8% compare to 31.5% & 30.4%) (p> 0.05). Common death rate is 37.25%, most are in inductionphase and intensification phase. The common cause of death is serious infection and bleeding. Relapse percentage is 16.7%.

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