STUDY ON THE CLINICAL AND LABORATORY FEATURES AND OUTCOME OF INDUCTION TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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ABSTRACT

Objective: *To study clinical and laboratory features and evaluate the outcome of treatment, to determine the recovery of peripheral blood cells and bone marrow cells after induction treatment of acute lymphoblastic leukemia (ALL) in children.*

Method: *A descriptive and retrospective study on 39 children diagnosed with ALL and treated in Pediatric Center, Hue Central Hospital from January 2012 to June 2015.*

Results: *The average age was 48 months old, mostly in the age group 12-60 months old (53.8%). Male /female ratio was 3.3/1.*

Clinical features: the rate of fever was 58.9%, the rate of fever with infectious sites was 33.3%. The rate of anemia was 92.3% (severe anemia: 23.1%, moderate anemia: 43.6%, mild anemia: 25.6%). The rate of mild and moderate hemorrhage was 48.7%. The rate of extramedullary infiltration was as follows: hepatomegaly: 87.2%, splenomegaly: 66.7%, enlarged lymph nodes: 33.3%.

Laboratory features: the number of bone marrow cells >100x10^9/mm^3: 51.3%, blast 58.5 ±15.53%. Lympho B: 84.4%, Lympho T: 15.6%.

Outcome: Complete remission: 89.7%, partial remission: 2.6%, death: 7.7%. There was a severe decrease in white blood cells from day 0 to day 7 and day 14 and the recovery was achieved from day 21 to day 28; The rate of severe decrease in neutrophils to less than 1x10^9/mm^3 in the first two weeks was 89.2%, the recovery was achieved at 2.03x10^9/mm^3 in day 28; the number of platelets was decreased in the first-two weeks and achieved at 246x10^9/mm^3 in day 28.

Conclusions: *After induction therapy: The rate of complete remission was rather high, mostly the number of peripheral blood cells decreased severely in the first-two weeks and recovered in 4 weeks.*

Key words: *Acute lymphoblastic leukemia, induction stage*

I. INTRODUCTION

Acute lymphoblastic leukemia (ALL), a malignant proliferative disease in lymphoid cell hematopoiesis, was the commonest type of cancer diagnosed in children [4], [10]. The initial diagnosis was based on clinical evidence such as anemia, infection, hemorrage, infiltration, the confirmed diagnosis was based on specific laboratory tests such as hemogram, myelogram, genetic abnormalities analysis... In recent years, the treatment of ALL has achieved many positive results [1], [5], [7]. However, the initial clinical manifestations were diverse, abundant, especially the signs of the onset sometimes were easily confused with the other diseases.

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Induction therapy was the first step in the treatment course and the period of multidrug combination in chemotherapy causing medullary insufficiency to put the patients into complete remission. Therefore, despite of one – month induction therapy course, the outcome was not always positive. Some patients got severe clinical manifestations and died because of severe complications of medullary insufficiency. Some patients were unresponsive or poorly responsive to treatment and needed many induction therapy courses to achieve complete remission.

Objective: To evaluate clinical and laboratory features and the outcome of induction therapy course of children with ALL treated at Pediatric Center, Hue Central Hospital.

II. SUBJECTS AND METHODS

2.1. Subjects: 39 patients confirmly diagnosed with ALL treated at the General Pediatrics n^0 2, Pediatric Center, Hue Central Hospital from January, 2012 to June, 2015.

2.2. Methods: Descriptive and retrospective study on 39 patients eligible for diagnosis of ALL.

Eligibility

- Confirmed diagnosis with ALL (according to criteria of WHO classification in 2008): the rate of medullary or blood immature white blood cells (WBC) was equal to or greater than 20% of nucleated cells, the lymphoblasts overwhelmed the normal hematopoietic lines [12].

Exclusion

- ALL secondary to other cancers.

- The patients in whom myelograms were not performed before and after induction therapy course.

- The patients had been treated before or voluntarily gave up and did not complete induction therapy course (except for death since the moment of diagnosis).

Study process

- **Clinical features:** evaluated of the infectious syndrome : fever and infectious sites; the extent of anemia : mild, moderate and severe; the extent of hemorrage: mild, moderate and severe and the situation of organ infiltration.

- **Laboratory features**: Blood cell count or hemogram performed to determine the number of WBC per mm^3, the percentage of polymorphonuclear leukocytes, lymphocytes and blood Hb level.

- Severe neutropenia : neutrophils count under <1x10^9/mm^3, severe cytopenia : platelet count < 20x10^9/mm^3, normal platelet count ≥ 150x10^9/mm^3.

- Myelogram: Normal bone marrow cell count from 30.000 - 100.000/mm^3, bone marrow aplasia: bone marrow cell count < 30.000/mm^3, bone marrow hyperplasia: bone marrow cell count > 100.000/mm^3.

- Cellular immunology: B lymphocyte line or T lymphocyte

Treatment and evaluating outcome of induction therapy course

- **Induction therapy:** Applying protocol of induction therapy (protocol CCG- 1881 modified) for ALL at Pediatric Center, Hue Central Hospital (induction therapy course prolonged 28 days) [6]

- The outcome:

- Criteria of complete remission: no symptoms clinically, no lymphoblasts, recovery of blood cell lines; hemogram with < 5% lymphoblast, recovery of other medullary cell lines on myelogram.

- Criteria of incomplete remission (partial): clinical symptoms improved in comparison to those at admission, but the number of lymphoblasts were still ≥ 5% of bone marrow cells count.

- Criteria of non - remission: clinical symptoms not improved, or worsened, the number of lymphoblasts > 25% of bone marrow cells count.

- The recovery and response of bone marrow and peripheral blood on day 7, 14, 21, 28.

- Death: rate, moment, duration, causes, clinical symptoms

III. RESULTS AND DISCUSSIONS

From January, 2012 to June, 2015 there was 39 patients diagnosed with ALL according to WHO 2008 and under induction therapy of modified CCG 1881 protocol.

Age: The average age was 48 months old, mostly in the age group 12-60 months old (53.8%).

Sex: Male: 30 cases (76.9%), female: 9 cases (23.1%). Male – to female ratio was 3.3/1

Our results were shown to be equivalent to those of author B. N. Lan (2007) at National Pediatric Hospital (2007), in which on 97 patients, mostly in the age group 12-60 months old (49.5%) [1]. Stork L. C. (2010) studied on 2027 patients with ALL in the U.S. also remarked mostly in the age group 24-60 months old (69.2%) [11].

Almost national and international studies also remarked more male patients than female patients with ALL [1], [2], [11]. Our results were also nearly equivalent to those of other authors.

3.1. Clinical features at the moment of diagnosis

Table 3.1: Clinical features at the moment of diagnosis

Clinical features		n	%
Fever with infectious sites (13/39 cases)	Bone and joint	3	*23.1*
	Lower respiratory tract	4	***30.8***
	E.N.T.	3	*23.1*
	GI	2	*15.4*
	CNS	1	*7.7*
Fever without infectious sites (10/39 cases)		10	*25.6*
Anemia (36/39 cases)	Mild	10	25.6
	Moderate	17	43.6
	Severe	9	**23.1**
Hemorrhage (19/39 cases)	Mild	8	20.5
	moderate	11	28.2
Hepatomegaly		34	87.2
Splenomegaly		25	66.7
Enlarged lymph nodes		13	33.3
Renal infiltration		3	7.7
CNS infiltration		1	2.6
Bone infiltration		4	10.3

Main clinical manifestations of ALL were bone marrow infiltration due to proliferation of lymphoblasts overwhelming the other normal cell lines. Mostly patients manifested 4 main syndromes: anemia, hemorrage, infection and infiltration.

In our study, there was 60% cases with fever at admission. In which, fever with infectious sites occupied 33.3%, fever without infectious sites, 25.7%. In our study, common infectious site at admission was low respiratoty tract (30.8%). In 2015, H. T. P. Thao studied at n°2 Pediatric Hospital on 59 patients and remarked that there were 74.6% with fever at moment of diagnosis [3]. The study at Hue of author Nguyen Dac Luong in 2012 showed that fever was one of the commonest symptoms of ALL (54.1%) [2]. Fever could be due to cancer itself or infection with increased inflammation response. Infection appeared due to strong proliferation of bone marrow lymphoblasts causing remarkably neutropenia leading to decreased body's defense against pathogenic agents from external environment.

Anemia was one of the most common manifestations and lasted for many days and many months. Anemia syndrome often manifested early, anemia developed gradually and often the patients were admitted at the hospital in a situation of moderate anemia, severe anemia was less frequent, anemia was irreversible and often required blood transfusion. Our results showed high rate of anemia at the moment of admission and were equivalent to other author's results [1], [2].

In our study, hemorrage at the moment of admission occupied 48.7% and were only mild and moderate hemorrage. Our results were rather equivalent to author Bui Ngoc Lan's results (49.5%) [1], author H. T. P. Thao (2015) remarked 42.4% of patients manifesting hemorrage at the moment of diagnosis [3].

Common symptom groups due to extramedullary lymphoblast infiltration consisted of hepatomegaly (87.2%), splenomegaly (66.7%), enlarged lymph nodes (33.3%). The less common symptoms were renal infiltration (7.7%), bone pain (10.3%), central

nervous system infiltration (2.6%). In our study, we had no cases with skin and testicular infiltration at the moment of diagnosis.

According to us, extramedullary organ infiltration was one of the common symptoms in ALL. Equivalent remarks among many author's results were on common infiltrations such as in liver, spleen, lymph nodes, on less common ones such as kidney, bone, CNS, testicules... Extramedullary organ infiltration syndrome, according to us, was really valuable clinically, leaded the physicians in orienting diagnosis of ALL.

3.2. Laboratory features at the moment of diagnosis

Table 3.2. Laboratory features at the moment of diagnosis

Laboratory features		N	%	X ± SD	Median (25^{th}-75^{th})
Bone marrow cell count (10^9/L)	Decreased (<30)	2	5.1		120 (90-177)
	Normal (30-100)	17	43.6		
	Increased (>100)	20	51.3		
Bone marrow blasts (%)				58.5± 15.53	
Bone marrow platelet	With	9	23.1		
	Without	30	76.9		
Cellular immunology	Lympho B	27	84.4		
	Lympho T	5	15.6		
WBC (10^9/L)	<10	12	30.8		21(5.8-59)
	≥10- <50	16	41		
	≥50 – 100	2	5.1		
	>100	9	23.1		
Platelet count (10^9/L)	<20	8	20.5		40(23 - 75)
	20-<50	17	43.6		
	50-<100	9	23.1		
	100-<150	2	5.1		
	≥150	3	7.7		
Blood hemoglobin level (g/dL)	<6	4	10.3		8.3(7.4 - 9.5)
	≥6 - <9	21	53.8		
	≥9 - <11	11	28.2		
	≥11	3	7.7		

Neutrophil count (10^9/L)	<0.5	24	61.5		0.23(0 - 1.64)
	0.5-1	4	10.3		
	>1	11	28.2		

According to the litterature, bone marrrow cell counts of children with ALL could increase, decease or normal. The table 3.2. also showed the similar results. The lymphoblasts increased highly in the bone marrow, overwhelmed strongly the other bone marrow cell lines and the rate of absence of platelet on bone marrow specimen was very high. On the other side, if bone marrrow cell counts were normal or decreased, the rate of immature cells was not high, it is necessary to differentiate with the other cancers spreaded to the bone marrow. The other studies also had similar results to ours [1], [2], .

We found 3 cell lines of peripheral blood decreased. In other studie's results, the rate of patients with WBC <10x10^9/mm^3 occupied highestly, and we also found the similar results. However, the rate of WBC >100x10^9/mm^3 in our study and Bui Ngoc Lan study's results were rather similar and both higher than the rates in foreign author's studies [4], [8]. This may be due to our sample was not big enough and most of our patients were examined and had ALL detected later so the proliferation rate of peripheral blood leukocyte count was very high. According to international authors, leukocyte count > 100x10^9/mm^3 was bad predictor which needed to be treated more aggressively with the circulation stagnation due to leukocytosis.

Hemorrhage syndrome and coagulation disorders were those of common clinical manifestions of ALL, whose cause was thrombocytopenia. In our study, platelet count of most patients decreased moderately, was 40x10^9/mm^3 (ranged from 23-75x10^9/mm^3). Patients with decreased severely platelet count (< 20x10^9/mm^3) whose rate was 20,5% often had risks of cerebral hemorrhage, lung hemorrhage and need to be perfused with cubed platelets aggressively to reduce mortality rate before chemotherapy. In comparison to author Bui Ngoc Lan's results (2007) (47x10^9/mm^3) (ranged from 1- 436 x10^9/mm^3), our results were also similar[1].

3.3. Outcome of induction therapy course

Table 3.3: Response after induction therapy course

Treatment response	n	%
Complete remission	35	**89.7**
Partial remission	1	2.6
Non – remission	0	0
Death	3	7.7
Sum	39	100

The progress in risk classification of children with ALL as well as in specific treatment protocol and enhanced supportive treatment protocol brought many achievements in management of ALL in children nowadays. The rate of patients with complete remission in our study was rather similar to those of national authors. Bui Ngoc Lan study's results (2008) showed the rate of patients with post – induction complete remission among 98 non – high risk cases was 87.8%, there was 12 patients died during induction course [1]. Our study and Nguyen Dac Luong's study (2012) used the same treatment protocol, however, he found a very high complete remission (97.3%), one case died (2.7%) [2], because he just studied on non – high risk subjects.

The studies of international authors also found very high complete remission rates (>95%): Pui C. H. (2010) with SJCRH 13B on 247 patients from 0-18 years old found 98% as the complete remission rate [10]. Author Moghrabi's study (2007) found there were 98% patients with post – induction complete remission, in which 4 died and 7 did not finished treatment course [9].

Table 3.4: The treatment recovery of some bone marrow cells

Characteristics		Day 0 (n=39)		Day 28 (n=36)	
		N	%	N	%
Bone marrow cell count	Decreased (<30x10⁹/L)	2	*5.1*	10	*27.8*
	Normal (30-100x10⁹/L)	17	*43.6*	25	***69.4***
	Increased (>100 x10⁹/L)	20	*51.3*	1	*2.8*
	Median (25th-75th)	120 (90-177)		33.4 (25-50)	
	p	p<0.05			
Immature white cell of the bone marrow	<5%	0	0	35	97.2
	≥5%	39	100%	1	**2.8**
	Median	55		0	
	p	p<0.01			
Platelet count	With	9	23.1	33	**91.7**
	Without	30	76.9	3	8.3

According to table 3.4, the rate of normal bone marrow cell count post – treatmently increased in comparison to that pre- treatmently. The median of the rate of immature white cell of the bone marrow decreased remarkably from day 0 in comparison to day 28, significantly statistically (p<0.05). Most bone marrow specimens on day 28 always had platelet counts (91.7%).

Table 3.5: The treatment response of peripheral blood cells

WBC(10⁹/L)	Day 0 (n=39)	Day 7 (n=37)	Day 14 (n=37)	Day 21 (n=36)	Day 28 (n=36)	p
	%	%	%	%	%	
≤1	0	10.8	29.7	2.8	**0**	
>1	100	89.2	70.3	97.2	100	
Median (25th-75th)	21 (5.8-59.0)	3.2 (1.3-8.1)	1.5 (0.9-3.7)	2.8 (2.0-4.1)	4.8 (3.1-6.2)	N0;N7<0.01 N0;N14<0.01 N0;N21<0.01 N0;N28<0.01

The rate of severely decreased white cell counts (<1x10⁹/L) increased gradually from day 0 to day 7, 14 and was 0 % on day 28.

Table 3.6: The treatment response of peripheral blood neutrophils

Neutrophils count (10⁹/L)	Day 0 (n=39)	Day 7 (n=37)	Day 14 (n=37)	Day 21 (n=36)	Day 28 (n=36)	p
	%	%	%	%	%	
<0.5	61.5	62.2	62.2	38.9	8.3	
0.5-1	10.3	8.1	27	19.4	11.1	
>1	28.2	29.7	10.8	41.7	80.6	

Median (25th-75th)	0.23 (0-1.6)	0.25 (0.1-1.2)	0.25 (0.1-0.6)	0.8 (0.2-2.5)	2.03 (1.1-3.7)	N0;N7>0.05 N0;N14>0.05 N0;N21<0.05 N0;N28<0.01

The rate of the patients with low absolute neutrophils counts decreased obviously from day 21 to day 28. The median of absolute neutrophils counts increased gradually from day 0 to day 28.

Table 3.7: The treatment response of peripheral blood platelets

Platelet count (10^9/L)	**Day 0** (n=39)	**Day 7** (n=37)	**Day 14** (n=37)	**Day 21** (n=36)	**Day 28** (n=36)	**p**
	%	%	%	%	%	
<20	20.5	16.2	8.1	2.8	0	
20-<50	43.6	27.0	29.7	8.3	0	
50-<100	23.1	27.0	35.1	13.9	2.8	
100-<150	5.1	13.5	8.1	19.4	13.9	
≥150	7.7	16.2	20	55.6	83.3	
Median (25th-75th)	40 (23-75)	53 (28.5-111)	59 (36-116.5)	172.5 (92.5-241.5)	246 (156.8-398.3)	N0;7>0.05 N0;14>0.05 N0;21<0.05 N0;28<0.01

The median of platelet count was lowest on day 0, increased gradually after each treatment week and returned to norms from day 21 to day 28. Only there was a difference between the median of platelet count of day 0 compared to that of day 21 and that of day 28 significantly statistically ($p<0.05$).

Table 3.8: The treatment response of peripheral blood Hb level

Level	**Mean± SD**	
Hb level at day 0	8.3 ±1.8 g/dL	p< 0.05
Hb level at day 28	9.4 ±1.5g/dL	

After induction treatment course, Hb level recovered significantly statistically ($p<0.05$).

In induction treatment course, many cytotoxic drug groups were used to suppress bone marrow in order to exclude immature leukocytes. Therefore, there was always suppression period of all components, bone marrow cell lines as well as peripheral blood cell'lines. After the treatment course, the components in bone marrow and peripheral blood would be suppressed decreasedly gradually and returned to normal activities, that was the recovery. In our study, we also found the recovery of some bone marrow cell lines in the induction treatment course, and our results were rather similar to those of other author's studies [1], [2].

Table 3.9: Causes and death moments

Death cases (n=3)	**Case 1**	**Case 2**	**Case 3**
Death moment	Day 3	Day 3	Day 14

Causes of death	Severe infection	X	X	X
	Severe electrolyte disorders		X	X
	Multi – organ failure			X
	CNS infiltration		X	

In our study, there was 3 cases of mortality during the induction treatment course which occupied 7,7%, in which 2 patients died on day 3 and 1 patient died on day 14. The cause of deaths was severe infection (100%).

The rate of mortality in our study was higher than that of Nguyen Dac Luong's study (2012) (2.7%) [2]. However, according to B. N. Lan's study (2007), the mortality rate in induction treatment course was high up to 12.2% [1]. In comparison to the international studies, the mortality rate in induction treatment course and overall mortality rate in our national studies were still high [7], [10]. This difference was due to the early examination and disease detection of foreign patients; morever, medical equipements and complications control process during treatment course were also better.

IV. CONCLUSIONS

Acute lmphoblastic leukemia in children manifested clinically and biologically rather abundantly with 4 main syndromes: anemia, infection, hemorrage and infiltration. The changements of bone marrow and peripheral blood cell components were due to the strong proliferation of immature leukocytes overwhelming the other normal cell lines. The induction treatment course would cause bone marrow insufficiency, cytopenia, neutropenia and thrombocytopenia. Bone marrow and peripheral blood cell lines decreased severely in 1 - 2 first treatment weeks, recovered after 4 weeks. The results of induction treatment course by modified CCG 1881 protocol were not so high complete remission rate due to rather high mortality rate. The main cause of mortality was severe infection during the 2 first treatment weeks.

It was necessary to expand the study in all treatment course and have a survival time follow – up to evaluate exactly and conclude more obviously the effectiveness of the protocol.

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