Original Research

STUDY ON CLINICAL, LABORATORY FEATURES AND THE RESULT OF MINIMAL RESIDUAL DISEASE AFTER INDUCTION PHASE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA AT HUE CENNTRAL HOSPITAL IN VIETNAM

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ABSTRACT

***Background**: Acute lymphoblastic leukemia (ALL) is the most common malignant disease in children. Mininal residual disease (MRD) levels after induction phase predict outcome and may select patients for therapy intensification.*

***Objective:** To analyse clinical presentations, laboratory features, especially the result of minimal levels in childhood acute lymphoblastic leukemia patients*

***Methods**: It was a prospective study on chilhood acute lymphoblastic leukemia patients who admitted hospital since April, 2018 to May, 2020.*

***Results:** There were 38 new patients, in which, 68.4% patients with standard risk, and 31.6% patients with high risk; the ratio of male to female was 2.16:1. The median age was 4.0 years (range: 0.66 to 15). The percentage of B-ALL, T-ALL and combined B and T- ALL were 81.6%, 15.8% and 2.6% respectively. The most common symptoms were anemia (86.8%), fever (76.3%), hepatomegaly (68.4%), splenomegaly (60.5%), enlarged lymph nodes (55.3%). For laboratory features, 26.4% patients had white blood cell (WBC) ≥ 50x10^9/l, 76.3% patients had platelet (PLT) < 100x10^9/l, 84.6% patients had blood hemoglobin level (Hb) < 10 g/dl. Lactate dehydrogenase (LDH) and C- reative protein (CRP) increased in most of patients, accounted for 89.5% and 73.7% respectively. After induction, complete remission which based on less than 5% blasts achieved 97.4%. However, MRD after induction phase with threshold ≤ 0.01% accounted for 78.9%. And based on MRD, we adjusted intensive chemotherapy for 4 patients.*

***Conclusion:** The most common clinical presentation was anemia, fever, hepatosplenomegaly, bone pain, bleeding. The result of MRD levels is more sensitive and precise to evaluate the responde after induction phase. Therefore, we could adjust intensitive therapy for some patients with high MRD levels to improve the treatment outcome.*

***Keywords:** Acute lymphoblastic leukemia, Mininal residual disease (MRD)*

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I. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignant disease in children. It accounts for one-fourth of all childhood cancers and 72% of all cases of childhood leukemia. The incidence is about 2 to 5 per 100.000 children. The peak incidence of ALL occours between 2 to 5 year of age. Outcome in acute lymphoblastic leukemia in children has shown a steady improvement. Overall survival achieved in 95% in 2007, comparing 21% in 1960 in high-incomes countries.

Complete remission in children with acute lymphoblastic leukemia (ALL) is traditionally defined as less than 5% blasts by light microscopic examination of the bone marrow (BM) aspirate. The definition by light microscopy examination is limited since it is unable to distinguish leukemic blasts from normal hematopoietic progenitor cells. Patients with ALL in remission may have varing levels of minimal residual disease (MRD) that is not detectable by light microscopy. Minimal residual disease (MRD) levels after induction phase predict outcome and could select patients for therapy intensification.

Hue Central Hospital plays an important role to treat childhood acute lymphoblastic leukemia in the central zone of Vietnam which covers geographically wide areas. Since 2008, ALL patients have treated by modified CCG 1961 & 1991 protocol. In order to improve the treatment outcome, we carry out this research to analyze the clinical presentations, laboratory tests, especialy the result of MRD levels after induction phase. Therefore, we could adjust intensify therapy for some patients to improve the treatment outcome.

II. PATIENTS AND METHODS

2.1. Patients

38 patients were diagnosed with acute lymphoblastic leukemia treated at Hue Pediatric Center- Hue Central Hospital, from April, 2018 to May, 2020.

2.2. Method

A prospective study: We described clinical presentations, laboratory tests and followed up the treatment.

Diagnosis of ALL at presentation was made on bone marrow morphology showed more than 20% leukemic blasts. Children were treated according to modified CCG 1991 & 1961 protocol. After induction phase, all patients were done bone marrow and checked MRD.

Data were analyzed according to age, gender, clinical presentations, laboratory tests, MRD levels, and the events happened during treatment.

Statistical analysis: Data were analyzed using Medcalc program.

III. RESULTS

A total of 38 new patients with acute lymphoblastic leukemia were identified from April 2018 to May 2020 and had enough eligible criteria. Of these, there were 26 males and 12 females, the ratio of male to female was 2.16:1. The median age was 4.0 years (range: 0.66 to 15). The peak incidence of ALL occoured in age group (1-< 10 years), with the percentage accounted 84.2%. The percentage of age group (< 1 year) and age group (≥ 10) were 2.6% and 13.2% respectively. They came from many different cities of central zone, in which, Hue and Quang Tri cities accounted 39.5% and 26.3% respectively (**table 1**).

Regarding clinical presentations: the median time since appearing symptoms to admitted hospital was 10 days (1-90). The most common symptoms were anemia (86.8%), fever (76.3%), hepatomegaly (68.4%), splenomegaly (60.5%), enlarged lymph nodes (55.3%). The other signs were bone pain, hemorrhage, respiratory distress and especially, there was one case with testicular involvement (2.65%) (**table 2**). For laboratory features, 26.4% patients had white blood cell (WBC) ≥ $50x10^9$/l, however, neutrophile was low, the median value was $0.41x10^9$/l (0-68.95x109/l). 76.3% patients had platelet (PLT) < $100x10^9$/l, 84.6% patients had blood hemoglobin level (Hb) < 10 g/dl. The median values of blast cells in bone marrow and peripheral blood were

56.5% (20-90) and 14% (0-79) respectively. Lactate dehydrogenase (LDH) and C- reative protein (CRP) increased in most of patients, accounted for 89.5% and 73.7% respectively. There was one case with renal failure and was recovered, accounted for 2.6% (**table 3**). In our patients, there were 68.4% patients with standard risk, and 31.6% patients with high risk. The percentage of B-ALL, T-ALL and combined B and T- ALL were 81.6%, 15.8% and 2.6% respectively. After induction, complete remission which based on less than 5% blasts achieved 97.4%. However, MRD after induction phase with threshold ≤ 0.01% accounted 78.9%.

And during treatment, there were two patients refused treatment after achieving remission, one patient passed away due to severe sepsis, three patient appeared relapse (one bone marrow relapse, one CNS relapse and one combined BM and CNS relapse). 84.2% patients are healthy and are receiving treatment (**table 4**).

Table 1: The general characteristics of patients

Characteristics	Number of patients	Percentage of patients (%)
Gender		
Male	26	68.4
Female	12	31.6
Median age (range)	4.0 (0.66 to 15)	
Age group		
< 1 year old	1	2.6
1- < 10 years old	32	84.2
≥ 10 years old	5	13.2
Patient's home town		
Hue	15	39.5
Quang Tri	10	26.3
Da Nang	4	10.5
Quang Nam	4	10.5
Quang Binh	2	5.3
Quang Ngai	1	2.6
Kon Tum	1	2.6
Phu Yen	1	2.6
Total	43	100

Table 2: Clinical presentations of patients

Clinical presentations	Number of patients	Percentage of patients (%)
Median time since appearing symptoms to admitted hospital	10 (1-90)	
Median fever (range) (^{0}C)	38 (37-40)	
Anemia	33	86.8
Fever	29	76.3
Hepatomegaly	26	68.4
Splenomegaly	23	60.5
Enlarged lymph nodes	21	55.3
Bone pain	12	31.6
Hemorrhage	11	28.9
Respiratory distress	2	5.3
Overt testiscular involvement	1	2.65
Total	43	100

Table 3: Laboratory features of patients

Laboratory features		Number of patients	Percentage of patients (%)	Median
WBC (x 10^9/l)	< 10	17	44.7	14.4 (1.8 -609.5)
	10 - < 50	11	28.9	
	≥ 50	10	26.4	
Neutrophile (x 10^9/l)				0.41 (0-68.95)
Platelet (x 10^9/l)	< 20	6	15.8	47.5 (3.0-223)
	20 - <100	23	60.5	
	≥ 100	9	23.7	
Blood hemoglobin level (g/dl)	< 6	9	23.7	7.15 (2.8-12.3)
	6- <9	20	52.6	
	9- < 10	2	5.3	
	≥ 10	7	18.4	
Peripheral blast cells				14 (0-79)
Bone marrow blast cell				56.5 (20-90)
Liver function	Increase	9	23.7	
	Normal	29	76.3	
Kidney function	Renal failure	1	2.6	
	Normal	37	97.4	
LDH	< 225	4	10.5	450 (205-7376)
	≥ 225	34	89.5	
Acid uric	< 460	31	81.6	268 (173 -1081)
	≥ 460	7	18.4	
CRP	≤ 8	10	26.3	14.5 (1.7-199.3)
	> 8	28	73.7	
CSF (Central spinal fluid)	2	38	100	

Table 4: Classify group and follow up treatment

Characteristics	Number of patients	Percentage of patients (%)
Classified risk group		
Standard	26	68.4
High	12	31.6
Immunophenotype		
B cell	31	81.6
T cell	6	15.8
B and T cells	1	2.6
After induction (evaluation based on blast cells)		
Remission	37	97.4
Not in remission	1	2.6
MRD after induction phase		
≤ 0.01%	30	78.9
> 0.01%	8	21.1
Events happened during treatment		
Abandonment	2	5.3
Death due to severe infection	1	2.6
Bone marrow relapse	1	2.6
CNS relapse	1	2.6
Bone marrow + CNS relapse	1	2.6

IV. DISCUSSION

Table 1 showed the ratio of male to female was 2.16:1 and the median age was 4.0 years old (0.66-15), which were similar with some other researches [1-7]. The higher proportion of age group (1- <10 years) (84.2%) has also been reported in Pakistan and Saudi-Arabia [1,6].

Hue Central Hospital plays an important role to treat childhood acute lymphoblastic leukemia in the central zone of Vietnam, so our patients came from different cities, not only in Hue (39.5%), but also from Quang Tri (26.3%), Danang, Quang Nam, Quang Binh, Quang Ngai, Kontum and PhuYen.

The most common clinical presentation in our group was anemia (86.8%), followed

by fever (76.33%), hepatomegaly (68.4%), splenomegaly (60.5%) and lymphadenopathy (55.4%). These clinical presentations were the same as those reported from Pakistan and they are common signs of acute lymphoblastic leukemia disease [1,7]. In our research, while the proportion of B-ALL was the predominant subtype (81.6%), at 15.8% there was a same percentage of T-cell ALL as the report from developed countries [1,6].

Regarding laboratory features, 26.4% of our patients had WBC counts ≥ 50x109/l, which was the same that reported in Pakistan [1], and was markedly higher that that reported in Western literature (17%), thus contributing to a higher tumor burden with a poorer outcome [8]. And it could be one of reason which cause LDH elevated. Almost our patients (89%) had elevated LDH. Beside, 76.3% our patients had PLT < $100x10^9$/l, and Hb < 9g/dl. There was no patient with CNS involvement, which was significant lower than that has been reported in Saudi Arabia (5% CNS3) [6]. Similar, the percentage of overt testicular involvement was lower (2.65% compare with 3.6%) [6].

After induction phase, 97.4% of our patients achieved complete remission. However, 78.9% of patients had MRD ≤ 0.01% and 21.1% had MRD > 0.01%. It could be explained that patients with ALL in remission may have varying levels of minimal residual disease (MRD) that is not detectable by light microscopy. It is estimated that patients who are in complete remission can harbor up to 10^{10} leukemic cells [9]. According to Vora, MRD ≥ 0.01% at the end of induction phase could benefit from augmented post-remission therapy [10]. Similar, Allen showed that minimal residual-guided treatment deintensification for children with acute lymphoblastic leukemia [11]. Therefore, for our patients, there were 4 patients with standard risk having MRD ≥ 0.01%, so we transferred him high risk group.

V. CONCLUSION

Childhood acute lymphoblastic leukemia are characteristic with anemia, thrombocytopenia, and neutropenia which in turn reflect the failure of normal hematopoiesis. The most common clinical presentation was anemia, fever, hepatosplenomegaly, bone pain, bleeding.

The result of MRD levels is more sensitive and precise to evaluate the responde after induction phase. Therefore, we could adjust intensify therapy for some patients with high MRD levels to improve the treatment outcome.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. This study was approved by the Hue Central Hospital Research Ethics Committee. **Animal subjects**: All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest**: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

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