Annals of Clinical and Analytical Medicine
Original Research

Clinical, laboratory features and minimal residual disease levels in childhood acute lymphoblastic leukemia at Hue Central Hospital, Viet Nam

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Abstract

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

In this study, we aimed to analyze the clinical presentations, laboratory features, especially the MRD levels in childhood acute lymphoblastic leukemia patients

Material and Methods: It was a prospective study on childhood acute lymphoblastic leukemia patients who admitted to the hospital between April-2018 and May-2020.

Results: There were 38 new patients, of whom, 68.4% were with standard risk, and 31.6% were 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 percentages of B-ALL and T-ALL were 84.2% and 15.8%, respectively. The most common symptoms were anemia (86.8%), fever (76.3%), hepatomegaly (68.4%), splenomegaly (60.5%), enlarged lymph nodes (55.3%). Regarding laboratory features, 26.4% of the patients had white blood cell (WBC) ≥ $50x10^9$/l, 76.3% had platelet (PLT) < $100x10^9$/l, 84.6% had blood hemoglobin level (Hb) < 10 g/dl. After induction, complete remission based on less than 5% blasts, achieved 97.4%. However, MRD after the induction phase with a threshold ≤ 0.01% accounted for 78.9%. Based on MRD, we adjusted intensive chemotherapy for 4 patients.

Discusssion: The most common clinical presentations were anemia, fever, hepatosplenomegaly, bone pain and bleeding. The MRD levels is more sensitive and precise to evaluate the response after the induction phase. Therefore, we could adjust intensive therapy for some patients with high MRD levels to improve the treatment outcome.

Keywords

Acute lymphoblastic leukemia; Minimal residual disease (MRD) levels; Children

DOI: 10.4328/ACAM.20328 Received: 2020-08-31 Accepted: 2020-10-02 Published Online: 2020-10-17
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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. Approximately 4,900 children are diagnosed with ALL each year in the United States, with an incidence of 2 to 5 cases per 100.000 U.S children. The peak incidence of ALL occurs between 2 to 5 years of age. The outcome in acute lymphoblastic leukemia in children has shown a steady improvement. Overall survival reached 95% in 2007, compared to 21% in 1960 in high-income countries.

Complete remission in children with ALL is traditionally defined as less than 5% blasts with 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 varying levels of minimal residual disease (MRD) that is not detectable by light microscopy. 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 been treated by the modified CCG 1961 & 1991 protocol. In order to improve the treatment outcome, we carry out this research to analyze the clinical presentations, laboratory tests, especially the result of MRD levels after induction phase. Therefore, we could adjust intensive therapy for some patients to improve the treatment outcome.

Material and Methods

Patients

Thirty-eight patients were diagnosed with ALL at Hue Pediatric Center- Hue Central Hospital from April- 2018 to May- 2020. All ethical regulations were followed, and this study was approved by the Hue Central Hospital Ethical Committee (Institutional Review Board No. 18/NCKH-BVH). Consent was obtained from all participants in this study.

Method

This is a prospective study. We described clinical presentations, laboratory tests and followed up the treatment.

Diagnosis of ALL on admission was made on the basis of bone marrow morphology, which showed more than 20% leukemic blasts. Children were treated according to the modified CCG 1991 & 1961 protocol. After the induction phase, all patients underwent bone marrow flow cytometry and MRD testing.

Data were analyzed according to age, gender, clinical presentations, laboratory tests, MRD levels, and the events that happened during treatment. All statistical analysis was performed using SPSS v.18.0 (IBM Corp, Armonk, NY).

Results

A total of 38 new patients with ALL were identified from April 2018 to May 2020 and met eligible criteria. Among these patients, 26 were males and 12 were females, the male to female ratio was 2.16:1. The median age was 4.0 years (range: 0.66 to 15). The peak incidence of ALL occurred in age group (1-< 10 years), accounted for 84.2%. The percentages of age group (< 1 year) and age group (≥ 10) were 2.6% and 13.2%, respectively (Table 3). Patient came from many different cities of the central zone: Hue (39.5%), Quang Tri (26.3%), Da Nang (10.5%), Quang Nam (10.5%), Quang Binh (5.3%), Quang Ngai, Kon Tum and Phu Yen had the same percentage (2.6%).

Regarding clinical presentations, the median time from the onset of symptoms to the hospital admission 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%). For laboratory features, 26.4% of the patients had white blood cell (WBC) ≥ $50x10^9$/l, however, neutrophil was low, the median value was $0.41x10^9$/l ($0-68.95x10^9$/l). 76.3% of the patients had platelet (PLT) < $100x10^9$/l, 84.6% had blood hemoglobin level (Hb) < 10 g/dl. The median values of blast cells in the 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, accounting for

Table 1. Treatment regimen for standard risk ALL: (modified CCG-1991)[1]

1. Induction: (1 month)
VCR 1.5mg/m² (max -2mg) - Days 0, 7, 14 and 21
DEX 6.0mg/m²/day - Days 0-27
L-Asp 6,000IU/m² for 9 doses (3 times weekly) starting on Day 3-5
IT MTX age 1 to less than 2 years, 8 mg
age 2 to less than 3 years,10 mg
older than 3 years, 12 mg - Days 0, 7*, 14, 21*, 28
* Patients with CNS disease at diagnosis only.
1.2. Consolidation: (1 month)
VCR 1.5mg/m² (max -2mg) - Day 0
6 MP 75mg/m²/day - Days 0-27
IT MTX on Days 7, 14**, 21**
** Patients with CNS disease at diagnosis will not receive IT therapy on days 14 & 21
1.3. Interim maintenance:
VCR 1.5mg/m² (max -2mg) - Days 0, 10, 20, 30, 40
MTX 100mg/m² starting dose- Days 0, 10, 20, 30, 40 (dose was escalated by 50mg/m2 every 10 days)
IT-MTX once on Day 0 and 30
1.4. Delayed Intensification: (49 days)
VCR 1.5mg/m² (max 2mg) - Days 0, 7 and 14
DEX 10 mg/m² - Days 0-6 and 14-20
L-Asp 6,000 U/m² for 6 doses x 2 times (days 3, 42)
DXR 25mg/m² - Days 0, 7 and 14
CPM 1,000mg/m² - Day 28
6 MP 75mg/m²/day - Days 28-41
Ara-C 75mg/m²/day - Days 28-31 and 35-38
IT MTX on Day 0 and 28
1.5. Maintenance: (84-day cycles ; 20 months)
VCR 1.5mg/m² (max-2mg) – every 28 days on Days 0, 28, 56
DEX 6 mg/m² -Days 0-4, 28-32, and 56-60
6 MP 75mg/m²/day - Days 0-83
MTX 20 mg/m² on day 7,14,21,28,35,42,49,56,63,70,77.
IT MTX once on Day 0

Note: VCR: Vincristine, DEX: Dexamethasone, L-asp: L-asparaginase; IT MTX: intrathecal methotrexate; 6 MP: 6-Mercaptopurin; DXR: Doxorubicine; CPM: Cyclophosphamide; Ara-C: Cytarabine.

Table 2. Treatment regimen for higher risk ALL: (modified CCG-1961)[2]

2.1. Induction:
VCR 1.5mg/m² (max -2mg) - Days 0, 7, 14 and 21
PSL 60mg/m²/day - Days 0-27
L-Asp 6000IU/m² for 9 doses (3 times weekly) starting on Day 3-5
DNR 25mg/m²/day - Days 0, 7, 14 and 21
IT MTX age 1 to less than 2 years, 8 mg
age 2 to less than 3 years,10 mg
older than 3 years, 12 mg - Days 0, 7*, 14, 21*, 28
* Patients with CNS disease at diagnosis only.
2.2. Consolidation: (9 weeks)
CPM 1000mg/m² - Days 0 and 28
6 MP 75mg/m² - Days 0-27
Ara-C 75mg/m²/day x 16 doses - Days 1-4, 8-11, 15-18, 22-25
VCR 1.5mg/m² (max 2mg) - Days 14, 21, 42 & 49
L-Asp 6000IU/m² x 12 doses (Monday, Wednesday, Friday) - beginning Day 14 (±1 day) and Day 42 (±1 day)
IT MTX on Days 0, 7, 14*, 21*
* Patient with CNS disease at diagnosis will not receive IT therapy on days 14 and 21.
2.3. Interim maintenance: (2 months)
MTX 100mg/m² - Days 0, 10, 20, 30, 40
VCR 1.5mg/m² (max -2mg) - Days 0, 10, 20, 30, 40
L-Asp 15000IU/m² - Days 1, 11, 21, 31, 41
IT MTX - Days 0, 20 and 40
2.4. Delayed Intensification: (2 months)
VCR 1.5mg/m² (max 2mg) - Days 0, 7, 14, 42, 49
DEX 10mg/m²/day - Days 0-20
L-Asp 6,000IU/m² x 6 doses - (Mon-Wed-Fri) Day 3-14, and (Mon-Wed-Fri) Day 42-53.
DXR 25mg/m² - Days 0, 7 & 14
CPM 1,000mg/m² - Day 28
6 MP 75mg/m²/day - Days 28-41
Ara-C 75mg/m²/day - Days 29-32 & 36-39
IT MTX - Days 29 and 36
2.5. Maintenance: (12-week (84-day) cycles)
VCR 1.5mg/m² (max-2mg) - Days 0, 28, 56.
PSL 40mg/m²/day - Days 0-4, 28-32, 56-60.
MTX 20mg/m²/week* - Day 7,14,21,28,35,42,49,56,63,70,77.
6 MP 75mg/m²/day* - Days 0-83.
IT MTX- Day 0 on each cycles
Note: * Doses escalated for ANC > 2,000 and platelet count ≥ 100,000. DNR: Daunorubicine.

89.5% and 73.7%, respectively. There was one case with renal failure which recovered (2.6%).

Among our patients, there were 68.4% of patients with standard risk, and 31.6% patients with high risk. The percentages of B-ALL and T-ALL were 84.2% and 15.8%, respectively. After induction, complete remission based on less than 5% blasts, achieved 97.4%. However, MRD after the induction phase with a threshold ≤ 0.01% accounted for 78.9%.

During the treatment, two patients refused treatment after achieving remission, one patient passed away due to severe sepsis, and three patients had 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 3. 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
Total	43	100

Discussion

Table 3 shows that the male to female ratio was 2.16:1 and the median age was 4.0 years old (0.66-15), which is similar to some other researches [3-9]. The higher proportion of age group (1- <10 years) (84.2%) has also been reported in Pakistan and Saudi-Arabia [3, 8].

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

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 similar to those reported from Pakistan and they are common signs of acute lymphoblastic leukemia disease [3, 9]. In our research, while the proportion of B-ALL was the predominant subtype (84.2%), 15.8% had the same percentage of T-cell ALL as the report from developed countries [3, 8].

Regarding laboratory features, 26.4% of our patients had WBC counts ≥ $50x10^9$/l, similar to what was reported in Pakistan [3], and was markedly higher than that reported in the Western literature (17%), thus contributing to a higher tumor burden with a poorer outcome [10]. And it could be one of the reasons for the increase in LDH. Almost all our patients (89%) had elevated LDH. Moreover, 76.3% of our patients had PLT < $100x10^9$/l, and Hb < 9g/dl. There was no patient with CNS involvement, which was significantly lower than that reported in Saudi Arabia (5% CNS3) [8]. Similarly, the percentage of overt testicular involvement was lower (2.65% compared to 3.6%) [8].

After the 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 by the fact 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 1010 leukemic cells [11]. According to Vora, MRD ≥ 0.01% at the end of the induction phase could benefit from augmented post-remission therapy [12]. Similar, Allen showed minimal residual- guided treatment deintensification for children with acute lymphoblastic leukemia [13]. Therefore, among our patients, 4 had a standard risk of

having MRD ≥ 0.01%, thus we transferred them to a high risk group.

Conclusion

The most common clinical presentations of acute lymphoblastic leukemia were anemia, fever, hepatosplenomegaly, bone pain, bleeding, which in turn reflected the failure of normal hematopoiesis.

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

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Nguyen Thi Kim Hoa, Phan Hung Viet, Tran Kiem Hao, Bui Binh Bao Son. Clinical, laboratory features and minimal residual disease levels in childhood acute lymphoblastic leukemia at Hue Central Hospital, Viet Nam. Ann Clin Anal Med 2020; DOI: 10.4328/ACAM.20328