

DEATH ANALYSIS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA AT HUE CENTRAL HOSPITAL IN VIETNAM

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ABSTRACT

Backgrounds: Outcome of acute lymphoblastic leukemia in children has shown a steady improvement, especially in high-income countries. However, the majority of children with acute lymphoblastic leukemia live in developing countries, where the cure rate is far lower.

Objective: To analyze the common cause of death in childhood acute lymphoblastic leukemia patients.

Method and Patients: A retrospective descriptive study on children with acute lymphoblastic leukemia who died at Hue Central Hospital since 2008 to 2016.

Results: Of 74 deaths, the ratio of male/female = 2.7/1. Diagnosis ranged between 6 months to 15 years, average 5.5 ± 4.4 years. High risk group is rate is twice as high as that of standard group (67.6% vs 32.4%). The initial WBC count at presentation was less than $50 \times 10^9/l$ in 48 (64.9%). The mean interval time since appearance of symptoms to hospital admission was 9.0 ± 18.4 days. At the time of death, 48 (64.9%) patients were in remission, while 26 (35.1) were not in remission. Of these 74 deaths, 26 (35.1%) occurred in maintenance phase, 18 (24.3%) occurred in induction phase, 9 (12.2%) occurred in delayed intensification. Infection was responsible for deaths in 32 of 74 (43.2%) cases. Relapse, abandonment and bleeding were documented in 20 (27.0%), 7 (9.5%) and 6 (8.1%) cases respectively. Of 32 infectious deaths, pneumonia occurred in 40.6% of the deaths. Regarding 20 relapse death, bone marrow was the major site of relapse, it occurred in 13 (65%) cases. And there were 65% patients with very early relapse.

Conclusion: Infection is the major cause of mortality in ALL patients in our study. To improve outcome, we should improve supportive care, especially in creasing quality of infection prevention and control.

Keywords: Acute lymphoblastic leukemia, death, infection.

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 is between 2 to 5 year of age [5].

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. This has been achieved through a combination of understanding the disease process better, identification of risk factors predicting a poor outcome and risk-stratified treatment of patients. Advances in supportive care such as antibiotics, antifungal treatment, blood banking, and availability of salvage options such as allogenic stem cell transplant have further improved the survival [6].

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However, the majority of children with ALL live in low-income countries, where the chance of a cure is far lower. The reason related death in these countries include: infections, hemorrhage, delay in diagnosis, chemo-drugs shortages, abandonment of therapy, chemotherapy induced toxicity, relapse.

Hue Central Hospital plays an important role in treating childhood acute lymphoblastic leukemia in the central region of Vietnam. Since 2008, ALL patients have been treated following CCG 1882&1881 protocol (a modified CCG protocol). In order to improve the treatment outcome, we conduct this research in order to: analyze the common cause of death in childhood acute lymphoblastic leukemia patients so, we can find the way to improve the treatment outcome.

II. PATIENTS MATERIALS AND METHODS

2.1. Patients

We review the medical records of pediatric patients who were treated for acute lymphoblastic leukemia between the ages 1 months and 16 years old, registered at Hue Pediatric Center- Hue Central Hospital, between 1st January 2008 and 30th June 2016. Medical records of the patients who died during this period were further analyzed for the purpose of this study.

2.2. Methods

A descriptive retrospective study: We collected the data of patients with pediatric acute lymphoblastic leukemia who were treated at Hue Pediatric Center and passed away.

Diagnosis of ALL at the presentation was based on bone marrow morphology which showed more than 25% leukemic blasts.

Children were treated according to CCG 1882&1881 protocol.

The protocol risk stratified patients according to age and initial white cell count. The criteria of standard risk are: Age between 1 and < 10 years old, initial WBC < 50.000/l. The criteria of high risk are: age ≥ 10 years old or < 1 year old, initial WBC ≥ 50.000/l.

Data were analyzed according to age, gender, initial white blood cell count, platelet, CRP, the

temperature, hospital to refer, disease status, timing of death, timing of relapse.

Statistical analysis: Data was analyzed using Medcalc program.

III. RESULT

3.1. Characteristics of patients

Table 1: Patient characteristics

Characteristics	n	%
Gender		
Male	54	73
Female	20	27
Median age, year range	5.5 ± 4.4 (0.5 – 15)	
Age group		
< 1	4	5.4
1- < 10	50	67.6
≥ 10	20	27.0
Classified risk group		
Standard	24	32.4
High	50	67.6
Immunophenotype		
B cell	52	70.3
T cell	22	29.7
Initial WBC count		
< 50.000	48	64.9
≥ 50.000	26	35.1
Treatment with steroid before refer to Hue Central Hospital		
Yes	3	4.1
No	71	95.9
Interval time since appearing symptoms to admitted hospital 9.0 ± 18.4		

Number of male were twice as high as that of female (73% vs 27%). The average age was 5.5 ± 4.4 years. Sixty seven point six percent

Hue Central Hospital

of the patients (67.6%) were between 1 to < 10 years. High risk group percentage was twice as high as that of standard group (67.6% vs 32.4%). Immunophenotyping confirmed that: ratio the initial WBC count at presentation was less than $50 \times 10^9/l$ in 48 (64.9%). Most of patients didn't use steroid before being referred to Hue Central Hospital (95.9%). The interval time since appearing symptoms to admitted hospital was 9.0 ± 18.4 days.

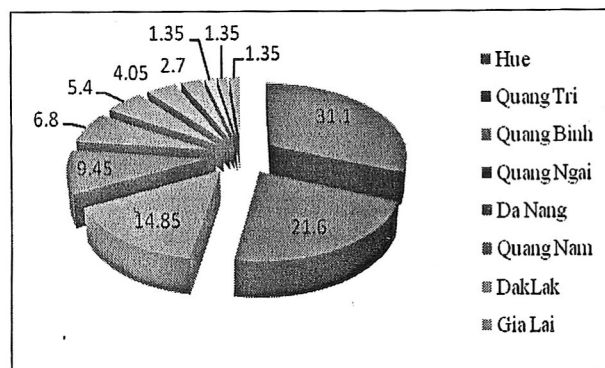


Figure 1: Hospital refer from

Most of patients come from Hue, Quang Tri and Quang Binh city, with the total percentage of 67.55%.

Table 2: The situation of family

Characteristic	n	%
Poor income	70	94.6
Poor education	66	89.2
Poor nutrition	41	55.4

94.6% patients were born in poor family income and the percentage of patients with poor family education had stayed at 89.2%.

3.2. Analyze the timing of death

Table 3: Timing of death with respect to protocol and status of death

Timing of death	n	%
Maintenance	26	35.1
Induction	18	24.3
Delayed intensification	9	12.2
Before initial of therapy	7	9.5
Interim maintenance	6	8.1

Consolidation	5	6.8
After induction	2	2.7
After treatment	1	1.4
Status of death		
Remission	48	64.9
Not in remission	26	35.1

At the time of death, 48 (64.9%) patients were in remission, while 26 (35.1%) were not in remission. Of these 74 deaths, 26 (35.1%) occurred in maintenance phase, 18 (24.3%) occurred in induction phase, 9 (12.2%) occurred in delayed intensification and 1 (1.4%) occurred after treatment.

3.3. Analyze the cause of death

3.3.1. The common cause of death

Table 4: The cause of death

The cause of death	n	%
Infection	32	43.20
Relapse	20	27.00
Abandonment	7	9.50
Bleeding	6	8.10
CNS disorders	3	4.10
Infection + Bleeding	2	2.70
Leukemia	2	2.70
Hyperleukocytosis	1	1.35
Heart failure	1	1.35
Total	74	100

Of 74 deaths, 32 (43.2%) patients died of infection, 20 (27.0%) died of relapse, 7 (9.5%) died of abandonment and 6 (8.1%) died of bleeding.

3.3.2. Analyze the cause of infection

Table 5: The reason of infection

The result of blood culture	n	%
Positive	3	9.4
Negative	29	90.6

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Site of infection		
Pneumonia	13	40.6
Intestinal infection	1	3.1
Ear infection	1	3.1
Other infection	17	53.2
Total	32	100
Median — CRP, range	115.2 ± 110.7 (10.3 – 402)	
Median Platelet count	12.500 ± 31.655 (2000 – 150.000)	
Temperature	39 ± 0.8 (37.8 – 40.5)	
ANC < 500	27	84.3

Of 32 infectious death, pneumonia occurred 40.6%. There were 9.4% patients with positive blood culture (*Pseudomonas aeruginosa*). At the time of death, 84.3% patients had ANC < 500.

3.3.3. Classify the site and time of relapse

Table 6: Classify the site and time of relapse

The site of relapse	n	%
Bone marrow	13	65
BM + CNS	4	20
Extramedullary	3	15
Time of relapse		
Very early relapse	13	65
Early relapse	1	5
Late relapse	6	30
Total	20	100

Of 20 relapse death, bone marrow was the major site of relapse, it occurred in 13 (65%) cases. And there were 65% patients with very early relapse.

IV. DISCUSSION

4.1. Characteristic of patients

Table 1 showed male were more two times higher than female (73% vs 27%). According to Muhammad Asim's research and Sumit Gupta's research, the male/female ratio was 1.24/1 and 1.29/1 respectively [4],[6]. Similarly, some other researches also showed that the incidence of ALL

was higher among boys than girls and male sex was a distinctly poor prognosis factor [6].

To age group: Sixty seven point six (67.6%) were between 1 to < 10 years. It was reasonable because the peak incidence of ALL occurs between 2 and 5 years of age [5]. Regarding classification of ALL, the majority of pediatric ALL cases express markers that indicate origin from an early B cell progenitor [5]. This result was similar with our study that showed 70.3% had B cell.

Most of our patients came from families with poor income, poor education and the interval time since appearing the first symptoms to admitted hospital were long (9.0 ± 18.4 days), so high risk group were more two times higher than standard group (67.6% vs 32.4%) in our study.

4.2. Analyze the timing and the cause of death

In our study, treatment related mortality occurred mainly during the maintenance phase (35.1%), even though they had achieved complete remission. Contrast to this, one research in America showed that the treatment related mortality occurred mainly during remission induction therapy (59%) [7]. The reasons might probably be that leukemia patients receiving chemotherapy were vulnerable, and caught neutropenia easily, especially when we gave high dose 6 MP (75mg/m^2). Besides that, when the patients had fever, they didn't come to hospital immediately. And sometimes we didn't give antibiotic reasonably, especially at the weekend when oncologist weren't on duty.

In the present study, infection were responsible for 43.2% deaths and 27/32 (84.3%) were neutropenic with ANC < 500. And pneumonia accounted for 40.6% of infectious death. Other groups have reported similar results. Choudhry et David showed that infection alone was responsible for death 47.3% and 68% cases respectively [1], [2]. Similarly, Muhammad et al from Pakistan found that infection alone or in combination with other factors was responsible for 85% death and 83% were neutropenic with ANC < 500 [4].

In our study, there were 9.4% infectious death with positive blood culture (*Pseudomonas*

aeruginosa). Contrast to this, Muhammad showed that 48.6% of all positive isolated were gram negative organisms while another 27% were gram positive organisms [4]. Similarly, Greenberg reported gram negative bacteria in 65%, gram positive bacteria in 30%. The reason might be our blood culture's techniques wasn't good enough.

The major non-infective causes of death in leukemic patients were relapse, abandonment and bleeding: 20 (27.0%), 7 (9.5%) and 6 (8.1%) cases respectively. Regarding bleeding, there are some similar results. Choudhry et al and Muhammad found hemorrhage accounted for 12.7% and 10.8% of death respectively. However, Choudhry et al and Muhammad didn't find any abandonment and relapse during they did research [1], [4]. Contrast to these researches, Traustiet al showed there were 18.9% relapse and the 5 year overall for patients relapsing was $57.3 \pm 3.4\%$ [8]. For our patients, most of them came from family with poor income, sometime, they didn't have enough money to cover the treatment. With the support

from ACCL, the abandonment rate was decrease. And at our department, we haven't used high dose methotrexate yet, so the patient can get relapse [3]. And when patients get relapse, we haven't done hematopoietic stem cell transplantation yet, or we don't have new agents in the treatment of relapse, so we can't save the children.

V. CONCLUSION

Infection remained the major cause of mortality in children with acute lymphoblastic leukemia (43.2%). And pneumonia occurred 40.6% of infectious death. The major non-infective causes of death in leukemic patients were relapse, abandonment and bleeding: 20 (27.0%), 7 (9.5%) and 6 (8.1%) cases respectively. In order to improve outcome, we should improve supportive care, especially prevention and control infection well, providing enough blood products, supporting finance for their families. In addition, we also consider using high dose methotrexate, and further some new therapies.

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