Causes of Death in Childhood Acute Lymphoblastic Leukemia at Hue Central Hospital for 10 Years (2008-2018)

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Abstract

Aim. To analyze the common cause of death in childhood acute lymphoblastic leukemia patients. Methods and Materials. A retrospective descriptive study on children with acute lymphoblastic leukemia who died at Hue Central Hospital between 2008 and 2018. All the patients were treated with the same protocol of modified Children’s Cancer Group 1882 and 1881. Results. A total of 238 children with acute lymphoblastic leukemia who were cared for at our center were enrolled. Of these, there were 74 deaths. Among the death group, the male-to-female ratio was 2.7:1. Twenty-six (35.1%) occurred in maintenance phase, 18 (24.3%) occurred in induction phase, and 9 (12.2%) occurred in delayed intensification. Infection was responsible for deaths in 32 of 74 (43.2%) cases. Pseudomonas aeruginosa was found in 3 of 32 infected cases (9.4%) and resistance to almost all antibiotics in our hospital. Relapse, abandonment, and bleeding were documented in 20 (27.0%), 7 (9.5%), and 6 (8.1%) cases, respectively. Twenty-seven (84.3%) patients had absolute neutrophil count <500/µL. Of 32 infectious deaths, pneumonia occurred in 40.6%. Regarding 20 relapse death, bone marrow was the major site of relapse and it occurred in 13 (65%) cases. And there were 65% patients with very early relapse. Conclusions. Infection is the major cause of mortality in acute lymphoblastic leukemia patients in our study. To improve outcome, we should improve supportive care, especially prevention and control infection.

Keywords

acute lymphoblastic leukemia, death, infection

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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. The incidence is about 2 to 5 per 100,000 children. The peak incidence of ALL occurs between 2 and 5 years of age.

Outcome in ALL in children has shown a steady improvement. Overall survival achieved in 95% in 2007, compared with 21% in 1960 in high-income 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. However, the majority of children with ALL live in low-income countries, where the chance of a cure is far lower. The reason related to death in these countries include infections, hemorrhage, delay in diagnosis, chemo-drugs shortages, abandonment of therapy, chemotherapy-induced toxicity, and relapse.

The Hue Central Hospital plays an important role to treat childhood ALL in the central zone of Vietnam, which covers geographically wide areas. Since 2008, ALL patients have been treated by modified Children’s Cancer Group (CCG) 1882 and 1881 protocol. Also, the
hospital has been receiving support from Asian Children’s Care League (ACCL), which provides safe food, financial support, housing for parents, and holding family group. With those special supports, treatment has been improving. In order to improve the treatment outcome, we carried out this research to analyze the common cause of death in childhood ALL patients. Therefore, we can find the way to improve treatment outcome.

**Subjects and Methods**

**Patients**

We reviewed the medical records of pediatric patients treated for ALL between the ages 1 month and 16 years, registered at the Pediatric Center, Hue Central Hospital, from January 1, 2008, to June 30, 2018. Medical records of the patients who died during this period were further analyzed for the purpose of this study. All ethical regulations were followed, and this study was approved by the Hue Central Hospital Ethical Committee (Institutional Review Board No. HCH01012008).

**Methods**

This was a retrospective cohort study using the data of pediatric ALL patients who were treated at Pediatric Center and passed away. Diagnosis of ALL at presentation was made on bone marrow morphology that showed more than 25% leukemic blasts.

Children were treated according to the modified CCG 1882 and 1881 protocol in which methotrexate (MTX) dose was decreased at interim maintenance phase for standard risk (Table 1). Our hospital has a children oncology department with 69 wards and also has an intensive care unit for all pediatric children, not only for children with cancer. All patients received trimethoprim-sulfamethoxazole prophylactic to prevent pneumocystis carinii, no antibiotic and antifungal prophylactics, and intensive treatment was provided whenever infection occurred, and the treatment included antibiotics ceftazi-dime, amikacin, meropenem, vancomycin and the anti-fungal amphotericin B. Transfusion of red blood cell is done when hemoglobin is under 8 g/dL, and transfusion of platelet is done when the platelet count is under 10 (K/µL), or under 30 (K/µL) with hemorrhage.

The protocol risk stratified patients according to age and initial white blood cell (WBC) count. The criteria of standard risk are age between 1 and <10 years and initial WBC <50000/µL. The criteria of high risk are age ≥10 years or <1years and initial WBC ≥50000/µL.

Data were analyzed according to age, gender, initial WBC count, platelet, C-reactive protein, temperature, hospital to refer, disease status, timing of death, and timing of relapse. All statistical analysis was performed using SPSS v.18.0 (IBM Corp, Armonk, NY).

**Results**

A total of 238 pediatric patients with ALL were identified for 10 years (2008-2018). Of these, there were 74 deaths. Cumulative mortality rate was 31.1% at 10-year follow-up. In the death group, males were more than 2 times higher than females (73% vs 27%). The average age was 5.5 ± 4.4 years. A total of 67.6% were between 1 and <10 years. The high-risk group is more than 2 times higher than the standard group (67.6% vs 32.4%). Immunophenotyping confirmed that 52 (70.3%) had B-cell and 22 (29.7%) had T-cell lymphomas. The initial WBC count at presentation was less than 50000/µL in 48 (64.9%) patients. Most of the patients did not use steroid before referring to Hue Central Hospital (95.9%). The interval time since appearing with symptoms to hospital admission was 9.0 ± 18.4 days. A total of 94.6% of the patients were born in low-income families, and the percentage of patients with poor family education was 89.2%. The patient characteristics are shown in Table 2. Most of the patients come from Hue, Quang Tri, and Quang Binh city, with a total percentage of 67.6% (Figure 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 the maintenance phase, 18 (24.3%) occurred in the induction phase, 9 (12.2%) occurred in the delayed intensification phase, and 1 (1.4%) occurred after treatment. Median time from diagnosis to death was 7.3 months (9 days to 56 months; Table 3). Of the 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 (Table 4). Of 32 infectious deaths, pneumonia occurred 40.6%. There were 9.4% patients with positive blood culture (*Pseudomonas aeruginosa*). At the time of death, 84.3% patients had absolute neutrophil count (ANC) <500/µL (Table 5). Of 20 relapse deaths, bone marrow was the major site of relapse and it occurred in 13 (65%) cases. And there were 65% of patients with very early relapse (Table 6).

**Discussion**

Table 2 showed that the ratio of males was more than 2 times higher than that of females (73% vs 27%). In our hospital, for children with cancer, the ratio of males was more than females at the initial diagnosis. According to Nguyen, a total of 403 new cases of childhood cancer
Table 1. CCG 1882 and 1881 Protocol.

1. Treatment regimen for standard risk ALL: (modified CCG 1881)

1.1 Induction (1 month)

| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| VCR       | 1.5 mg/m² (maximum 2 mg)        | 0, 7, 14, 21  |
| DEX       | 6.0 mg/m²/day                   | 0-27          |
| L-Asp     | 6000 IU/m² for 9 doses          | 2-4           |
| IT MTX    | Age < 2 years: 8 mg             |               |
|           | Age < 3 years: 10 mg            |               |
|           | Older than 3 years: 12 mg       |               |

*Patients with CNS disease at diagnosis only.

1.2 Consolidation (1 month)

| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| VCR       | 1.5 mg/m² (maximum 2 mg)        | 0             |
| 6-MP      | 75 mg/m²/day                   | 0-27          |
| IT MTX    | Days 0, 7, 14 a, 21 a           |               |

*Patients without CNS disease at diagnosis will not receive IT therapy on days 14 and 21.

1.3 Interim maintenance (56 days)

| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| VCR       | 1.5 mg/m² (maximum 2 mg)        | 0, 28         |
| MTX       | 20 mg/m²                        | 7, 14, 21, 28, 35, 42, and 49 |
| 6-MP      | 75 mg/m²                       | 0-55          |
| DEX       | 6 mg/m²/day                     | 0-4 and 28-32 |
| IT-MTX    | once on Day 0                   |               |

1.4 Delayed intensification (49 days)

<First phase>
| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| VCR       | 1.5 mg/m² (maximum 2 mg)        | 0, 7, and 14  |
| DEX       | 10 mg/m²                        | 0-20, then taper over 7 days |
| L-Asp     | 6000 IU/m² for 6 doses          | 2-4           |
| DXR       | 25 mg/m²                        | 0, 7, and 14  |

<Second phase>
| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| CPM       | 1000 mg/m²                      | 28            |
| 6-MP      | 75 mg/m²/day                    | 28-41         |
| Ara-C     | 75 mg/m²/day                    | 29-32 and 36-39 |
| IT MTX    | once on Days 28 and 35          |               |

1.5 Maintenance (84-day cycles; 20 months)

| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| VCR       | 1.5 mg/m² (maximum 2 mg)        | 0, 28, and 56 |
| DEX       | 6 mg/m²/day                     | 0-4, 28-32, and 56-60 |
| 6-MP      | 75 mg/m²/day                    | 0-83          |
| MTX       | 20 mg/m² on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77. |       |
| IT MTX    | once on Day 0 of each course    |               |

2. Treatment regimen for higher risk ALL: (modified CCG 1882)

2.1 Induction

| Drug      | Dosage                          | Days          |
|-----------|---------------------------------|---------------|
| VCR       | 1.5 mg/m² (maximum 2 mg)        | 0, 7, 14, and 21 |
| PSL       | 60 mg/m²/day                    | 0-27          |
| L-Asp     | 6000 IU/m² for 9 doses          | 2-4           |
| DNR       | 25 mg/m²/day                    | 0, 7, 14, and 21 |
| IT MTX    | Age < 2 years: 8 mg             |               |
|           | Age < 3 years: 10 mg            |               |
|           | Older than 3 years: 12 mg       |               |
| IT Ara-C  | Age < 2 years: 30 mg            |               |
|           | Age < 3 years: 50 mg            |               |
|           | Older than 3 years: 70 mg       |               |

(continued)
were admitted to Hue Central Hospital and Danang Mother and Children Hospital in Vietnam during April 2014 to July 2019, with a male-to-female ratio of 1.65:1. In the study by Chau,6 who did research on gene mutation on 50 acute leukemia patients, the male-to-female ratio was 2:1. And others in our country researching children with cancer also showed that males were predominant than females. We need some large studies to identify this. According to Asim et al7 and Gupta et al,8 the male-to-female ratio was 1.24:1 and 1.29:1, respectively. Similarly, some other reports also showed that the incidence of ALL was higher among boys than girls, and males has a distinctly poor prognosis factor.4

With regard to age group, 67.6% were between 1 and <10 years. It was reasonable because the peak incidence of ALL occurs between 2 and 5 years of age.3

Regarding classification of ALL, the majority of pediatric ALL cases express markers that indicate origin from an early B-cell progenitor.3 This result was similar with our study, which showed that 70.3% had B-cell lymphomas.

Most of our patients came from families with poor income and poor education. When some symptoms appeared in patients, they often came to pharmacies to buy medicines or brought them to local doctors, or let them take some herbal medicines, and if patients felt better, their parents did not bring them to hospital, until they were very tired. This was a reason why the interval time since appearing with first symptoms to hospital admission was long (9.0 ± 18.4 days). Therefore, the high-risk group was more than 2 times higher than the standard group (67.6% vs 32.4%) in our study.
In our study, treatment-related mortality occurred mainly during the maintenance phase (35.1%), even though the patients had achieved complete remission. In contrast to this, one research in the United States showed that treatment-related mortality occurred mainly during remission of induction therapy (59%). The reasons might probably be that leukemia patients receiving chemotherapy were vulnerable and caught neutropenia easily, especially when given high-dose mercaptopurine (6-MP; 75 mg/m²). Now, we are conducting 6-MP research, and we are finding some patients with TPMT and NUDT15 mutations, and patients are very sensitive to 6-MP. Besides that, when the patients had fever, they did not come to a hospital immediately. And the other problem was lack of pediatric oncologists and standard protocol for febrile neutropenia. In our hospital, there are 4 pediatric oncologists, so oncologists were not always in hospital, and other pediatricians did not give antibiotics reasonably.

In the present study, all the patients were intensively treated with antibiotics when they were suspected of infection. However, the time to provide antibiotics was sometimes late because admission to the hospital was late and due to lack of knowledge of pediatricians. And there were shortage of antibiotics and antifungals sometimes, which influenced the treatment of infection. Infection was responsible for 43.2% deaths, and 27/32

### Table 2. Patient Characteristics.

| Characteristics | All Patients (N = 74), n (%) |
|-----------------|-----------------------------|
| **Gender**      |                             |
| Male            | 54 (73%)                    |
| Female          | 20 (27%)                    |
| **Age, mean (range)** | 5.5 ± 4.4 (0.5-15)         |
| **Age group (years)** |                      |
| <1              | 4 (5.4%)                    |
| 1 to <10        | 50 (67.6%)                  |
| ≥10             | 20 (27%)                    |
| **Classify risk group** |              |
| Standard        | 24 (32.4%)                  |
| High            | 50 (67.6%)                  |
| **Immunophenotype** |                            |
| B-cell          | 52 (70.3%)                  |
| T-cell          | 22 (29.7%)                  |
| **Initial white blood cell count** |                    |
| <50,000/µL      | 48 (64.9%)                  |
| ≥50,000/µL      | 26 (35.1%)                  |
| **Treatment with steroid before referring to Hue Central Hospital** |       |
| Yes             | 3 (4.1%)                    |
| No              | 71 (95.9%)                  |
| **Interval time since appearance of symptoms to being admitted to hospital for the initial diagnosis** | 9.0 ± 18.4 days |
| **Family situation** |                                 |
| Poor income⁴   | 70 (94.6%)                  |
| Poor education⁵| 66 (89.2%)                  |
| Poor nutrition⁶ | 41 (55.4%)                  |

¹Monthly income earned was up to $31 in rural areas and $40 in cities.
²Did not reach high school level.
³Poor supplement foods in both quantity and quality. Poor nutrition was determined by body mass index.

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![Figure 1. Geographical distribution of patients.](chart)

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In the present study, all the patients were intensively treated with antibiotics when they were suspected of infection. However, the time to provide antibiotics was sometimes late because admission to the hospital was late and due to lack of knowledge of pediatricians. And there were shortage of antibiotics and antifungals sometimes, which influenced the treatment of infection. Infection was responsible for 43.2% deaths, and 27/32
(84.3%) were neutropenic with ANC <500/µL. And pneumonia occurred in 40.6% of infectious deaths. Other groups have reported similar results. Choudhry et al and O'Connor et al showed that infection alone was responsible for death in 47.3% and 68% cases, respectively.9,10 Similarly, Asim 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/µL.7

In our study, there were 9.4% infectious deaths with positive blood culture (Pseudomonas aeruginosa). Pseudomonas aeruginosa was resistance to almost antibiotics in our hospital. The following are the antibiotic and prevalence of resistance: colistin (10.7%), fosfomycin
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Infection remained the major cause of mortality in children with ALL (43.2%). And pneumonia occurred in 40.6% of infectious deaths. The major noninfective 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 have a systemic plan to educate families and staff on febrile neutropenia, compose standard protocol for febrile neutropenia, and improve supportive care. Our hospital should have standard criteria to provide enough blood products, provide enough chemo-agents, antibiotics, and antifungal, and also supporting finance for their families. In addition, we also consider using high-dose MTX and providing further new therapies.

**Conclusion**

Infection remained the major cause of mortality in children with ALL (43.2%). And pneumonia occurred in 40.6% of infectious deaths. The major noninfective 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 have a systemic plan to educate families and staff on febrile neutropenia, compose standard protocol for febrile neutropenia, and improve supportive care. Our hospital should have standard criteria to provide enough blood products, provide enough chemo-agents, antibiotics, and antifungal, and also supporting finance for their families. In addition, we also consider using high-dose MTX and providing further new therapies.

**Author Contributions**

TKH: Contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

PNH: Contributed to conception; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

NTKH: Contributed to conception and design; contributed to analysis; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

CVH: Contributed to conception; gave final approval.

**Declaration of Conflicting Interests**

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