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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.[1] It accounts for one fourth of all childhood cancers and 72% of all cases of childhood leukemia.[2] The incidence is about 2 to 5 per 100 000 children. The peak incidence of ALL occurs between 2 and 5 years of age.[3]

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.[4]

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

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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 ceftazidime, amikacin, meropenem, vancomycin and the antifungal 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 $<50\,000/\mu L$. The criteria of high risk are age ≥ 10 years or <1years and initial WBC $\geq 50\,000/\mu L$.

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 $50\,000/\mu L$ 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) $<500/\mu L$ (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,[5] 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)

VCR 1.5 mg/m^2 (maximum 2 mg)—Days 0, 7, 14, and 21
DEX 6.0 mg/m^2/day—Days 0-27
L-Asp 6000 IU/m^2 for 9 doses (3 times weekly) starting on Days 2-4
IT MTX:
Age 1 to <2 years, 8 mg
Age 2 to <3 years, 10 mg
Older than 3 years, 12 mg—Days 0, 7[a], 14, and 21[a]

[a]Patients with CNS disease at diagnosis only.

1.2. Consolidation (1 month)

VCR 1.5 mg/m^2 (maximum 2 mg)—Day 0
6-MP 75 mg/m^2/day—Days 0-27
IT MTX on Days 0, 7, 14[b], and 21[b]

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

1.3. Interim maintenance (56 days)

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

1.4. Delayed intensification (49 days)

<First phase>
VCR 1.5 mg/m^2 (maximum 2 mg)—Days 0, 7, and 14
DEX 10 mg/m^2—Days 0-20, then taper over 7 days
L-Asp 6000 IU/m^2 for 6 doses (3 times weekly) starting on Days 2-4
DXR 25 mg/m^2—Days 0, 7, and 14
<Second phase>
CPM 1000 mg/m^2—Day 28
6-MP 75 mg/m^2/day—Days 28-41
Ara-C 75 mg/m^2/day—Days 29-32 and 36-39
IT MTX on Days 28 and 35

1.5. Maintenance (84-day cycles; 20 months)

VCR 1.5 mg/m^2 (maximum 2 mg)—every 28 days on Days 0, 28, and 56
DEX 6 mg/m^2—Days 0-4, 28-32, and 56-60
6-MP 75 mg/m^2/day—Days 0-83
MTX 20 mg/m^2 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

VCR 1.5 mg/m^2 (maximum 2 mg)—Days 0, 7, 14, and 21
PSL 60 mg/m^2/day—Days 0-27
L-Asp 6000 IU/m^2 for 9 doses (3 times weekly) starting on Days 2-4
DNR 25 mg/m^2/day—Days 0, 7, 14, and 21
IT MTX:
Age 1 to <2 years, 8 mg
Age 2 to <3 years,10 mg
Older than 3 years, 12 mg—Days 7[c], 14, 21[c], and 28
IT Ara-C:
Age 1 to <2 years, 30 mg
Age 2 to <3 years,50 mg
Older than 3 years, 70 mg—Day 0

(continued)

Table 1. (continued)

[c]Patients with CNS disease at diagnosis only.

2.2. Consolidation (9 weeks)

CPM 1000 mg/m^2—Days 0 and 28
6-MP 75mg/m^2—Days 0-13 and 28-41
Ara-C 75 mg/m^2/day × 16 doses—Days 0-3, 7-10, 28-31, and 35-38
VCR 1.5 mg/m^2 (maximum 2 mg)—Days 14, 21, 42, and 49
L-Asp 6000 IU/m^2 × 12 doses (Monday, Wednesday, Friday)—beginning Day 14 (±1 day) and Day 42 (±1 day)
IT MTX on Days 0, 7, 14[d], and 21[d]

[d]Patient without CNS disease at diagnosis will not receive IT therapy on Days 14 and 21.

2.3. Interim maintenance (2 months)

MTX 100 mg/m^2—Days 0, 10, 20, 30, and 40
VCR 1.5 mg/m^2 (maximum 2 mg)—Days 0, 10, 20, 30, and 40
L-Asp 15000 IU/m^2—Days 1, 11, 21, 31, and 41
IT MTX—Days 0, 20, and 40

2.4. Delayed intensification (2 months)

VCR 1.5 mg/m^2 (maximum 2 mg)—Days 0, 7, 14, 42, and 49
DEX 10 mg/m^2/day—Days 0-20
L-Asp 6000 IU/m^2 × 6 doses—(Monday, Wednesday, Friday) Days 3-14, and (Monday, Wednesday, Friday) Days 42-53
DXR 25 mg/m^2—Days 0, 7, and 14
CPM 1000 mg/m^2—Day 28
6-MP 75 mg/m^2/day—Days 28-41
Ara-C 75 mg/m^2/day—Days 29-32 and 36-39
IT MTX—Days 29 and 36

2.5. Maintenance (12-week [84-day] cycles)

VCR 1.5 mg/m^2 (maximum 2 mg)—Days 0, 28, and 56
PSL 40 mg/m^2/day—Days 0-4, 28-32, and 56-60
MTX 20 mg/m^2/week[e]—Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77
6-MP 75 mg/m^2/day[e]—Days 0-83
IT MTX—Day 0 on each cycles

[e]Doses escalated for ANC >2000 and platelet count ≥100000.

Abbreviations: CCG, Children's Cancer Group; ALL, acute lymphoblastic leukemia; VCR, vincristine; DEX, dexamethasone; L-Asp, L-asparaginase; IT, intrathecal; MTX, methotrexate; CNS, central nervous system; 6-MP, mercaptopurine; CPM, cyclophosphamide; Ara-C, cytarabine; PSL, prednisolone; DNR, daunorubicin; DXR, doxorubicin; ANC, absolute neutrophil count.

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 al[7] 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.

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 income[a]	70 (94.6%)
Poor education[b]	66 (89.2%)
Poor nutrition[c]	41 (55.4%)

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

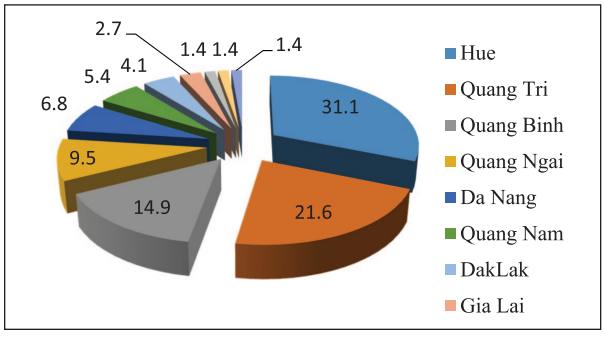

Figure 1. Geographical distribution of patients.

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%).[8] 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/m^2). 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 3. Timing of Death With Regard to Protocol and Status of Death.

Timing of Death and Status of Death	All Patients (N = 74), n (%)
Timing of death	
Maintenance	26 (35.1%)
Induction	18 (24.3%)
Delayed intensification	9 (12.2%)
Before initial 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%)
Time from diagnosis to death, median (range)	7.3 months (9 days to 56 months)

Table 4. The Cause of Death.

Cause of Death	All Patients (N = 74), n (%)
Infection	32 (43.2%)
Relapse	20 (27%)
Abandonment	7 (9.5%)
Bleeding	6 (8.1%)
Central nervous system disorders	3 (4.1%)
Infection + bleeding	2 (2.7%)
Leukemia (died prior to initiation of therapy)	2 (2.7%)
Hyperleukocytosis	1 (1.35%)
Heart failure	1 (1.35%)

Table 5. The Reasons for Infection.

Reasons for Infection	Infection Group (N = 32), n (%)
Result of blood culture	
Positive	3 (9.4%)
Negative	29 (90.6%)
Site of infection	
Pneumonia	13 (40.6%)
Intestinal infection	1 (3.1%)
Ear infection	1 (3.1%)
Other infection	17 (53.2%)
C-reactive protein (mg/L), mean (range)	115.2 ± 110.7 (10.3-402)
Platelet count (/μL), mean (range)	12 500 ± 31 655 (2000-150 000)
Temperature (°C), mean (range)	39 ± 0.8 (37.8-40.5)
Absolute neutrophil count <500/μL	27 (84.3%)

(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

Table 6. Classification of the Site and Time of Relapse.

Classification of the Site and Time of Relapse	Relapse Group (N = 20), n (%)
Site of relapse	
Bone marrow	13 (65%)
Bone marrow + central nervous system	4 (20%)
Extramedullary	3 (15%)
Time of relapse	
Very early relapse	13 (65%)
Early relapse	1 (5%)
Late relapse	6 (30%)

(24%), aztreonam (36%), amikacin (42.9%), ciprofloxacin (48.2%), cefepime (45.8%), imipenem (46.2%), gentamicin (55.6%), cefoperazone (54.2%), ticarcillin/clavulanic acid (54.2%), tobramycin (54.2%), piperacillin (60.7%), cefsulodin (62.5%), and sulfamides (64%). In contrast to this, Asim et al showed that 48.6% of all positives isolated were gram-negative organisms, while another 27% were gram-positive organisms.[7] Similarly, Greenberg et al reported gram-negative bacteria in 65% and gram-positive bacteria in 30%.[11] The reason might be that our blood culture techniques was not good enough.

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. Some patients appeared with bleeding due to low platelets, and the blood product support was not always readily available at our hospital. Several years ago, patients had to pay money for using platelets. Regarding bleeding, there are some similar results. Choudhry et al[9] and Asim et al[7] found hemorrhage accounted for 12.7% and 10.8% of deaths, respectively. However, these authors did not find any abandonment and relapse case during their research. In contrast to these researches, Oskarsson et al showed that there was 18.9% relapse and the 5-year overall survival for patients relapsing was 57.3 ± 3.4%.[12] For our patients, most of them came from families with poor income, so sometimes they did not have enough money to cover the treatment. With the support from nongovernmental organization ACCL, the abandonment rate decreased. However, some ethnic patients whose parents did not have good awareness sometimes refused treatment. And at our center, we have not used high-dose MTX yet, which may have led to relapse in patients.[13] Also, when patients have relapse, hematopoietic stem cell transplantation cannot be provided at our center yet, and we do not have new agents in the treatment of relapse to save the children.

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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