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

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ABSTRACT

***Background**: Treatment outcome of acute lymphoblastic leukemia (ALL) in children has shown an improvement. However, relapse of disease is still a big protslen in developing countries. This study aimed to analyze the percentage and survival rate of relapsed in patients with childhood acute lymphoblastic leukemia treated at Hue Central Hospital, Vietnam, during the period of January 2012 - April 2018.*

***Methods**: It was a retrospective and prospective descriptive study. Data were analyzed according to age, gender, relapse type, relapse time.*

***Results**: There were 156 new patients with ALL admitted hospital, in which, there were 26 relapsed cases, accounted for 16.67%. Of 26 relapsed cases, the ratio of male to female was 2.71:1. High risk group was 1.6 times higher than standard group (61.5% vs 38.5%). 85.5% of patients achieved remission after induction phase. The mean time from diagnosis to relapse was 29.3 ± 18.2 months, in which the rate of early, intermediate and late relapse were 38.5%, 26.9% and 34.6% respectively. Based on relapse timing, 53.8% of patients relapsed during maintenance phase, 23.1% relapsed after finishing therapy, 15.4% relapsed at delayed intensification phase and 7.7% relapsed after induction phase due to treatment abandonment. Based on relapse type, bone marrow relapse accounted 38.5%, followed by isolated CNS, bone marrow combined CNS relapse (23.1% and 23.1% for respectively), while the rest had a relapse in testes, combination of testis and bone marrow, and testis combined CNS. The median time from relapse to death were 7.5 ± 8.3 months. Until April 2018, 73.1% of relapsed cases passed away and 26.9% of cases were are alive.*

***Conclusions:** Most relapsed cases occurred at maintenance phase and after finishing treatment. Bone marrow and CNS were the main sites of relapse.*

***Key words:** Childhood acute lymphoblastic leukemia, relapse.*

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. With advances in chemotherapy, hematopoietic stem cell transplantation and supportive care, long-term survival in childhood acute lymphoblastic leukemia is now 85-90%. Despite increasing, concerns regarding treatment related mortality and second

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malignancies, the main reason for treatment failure is still relapse. The prognostic factors most important for determining survival post-relapse include: site of relapse (bone marrow vs. isolated extramedullary vs. combined), timing of relapse (early vs. late), phenotype of the original and recurrent disease, prognostic features characterizing the primary diagnosis and depth of response [2], [3], [4]..

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 1882 & 1881 protocol. In order to improve the treatment outcome, we carry out this research to analyze the incidence and survival rate of relapse in patients with childhood acute lymphoblastic leukemia treated at Hue Central Hospital, Vietnam, during the period of January 2012 - April 2018.

II. PATIENTS AND METHODS

2.1. Patients

We reviewed the medical records of pediatric patients 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 2012 to 30th April 2018. Medical records of the patients who were diagnosed relapse during this period were further analyzed for the purpose of this study.

2.2. Methods

A describe retrospective and prospective study: We collected the data of 156 new patients diagnosed acute lymphoblastic leukemia at Hue Pediatric Center, then we analysed and followed up 26 cases with relapse ALL.

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

Children were treated according to modified CCG 1882 & 1881 protocol.

Relapse events were defined by time from initial diagnosis (early: <18 months; intermediate: 18-36 months, late ≥ 36 months).

Data were analyzed according to age, gender, relapse type, relapse time.

Statistical analysis: Data were analyzed using Medcalc program.

III. RESULTS

3.1. The percentage of relapse rate

Table 1: The incidence of relapse rate

Characteristic	n	%
Relapsed patients	26	16.67
Non-relapsed patients	130	83.33
Total	156	100

Of 156 patients, relapsed cases accounted for 16.67%.

3.2. Characteristics of relapsed patients

Table 2: The characteristics of relapsed patients

Characteristics	n	%
Gender		
Male	19	73.1
Female	7	26.9

Classify risk group		
Standard	10	38.5
High	16	61.5
Achieved remission after induction phase		
Yes	23	88.5
No	3	11.5
Total	26	100

Male was more than two times higher than female (73.1% vs 26.9%). High risk group was higher than standard group (61.5% vs 38.5%). 88.5% of patients achieved remission after induction phase.

3.3. Time of relapse

Table 3: Time of relapse

Time of relapse	n	%
Early relapse	10	38.5
Intermediate relapse	7	26.9
Late relapse	9	34.6
Mean time, month range	29.3 ± 18.2	
Relapse timing		
Maintenance phase	14	53.8
Finishing treatment	6	23.1
Delay intensification II	4	15.4
Consolidation	2	7.7
Total	26	100

Of 26 relapsed cases: 14 (53.8%) occurred in maintenance phase, 4 (15.4%) occurred in delay intensification II phase, 2 (7.7%) occurred in consolidation, and 6 patients (23.1%) who completed treatment appeared relapse. The rate of early relapse was highest, then late relapse and intermediate relapse.

3.4. Site of relapse

Table 4: Site of relapse

Site of relapse	n	%
Bone marrow	10	38.5
CNS	6	23.1
Bone marrow + CNS	6	23.1
Testis	2	7.6
Testis + Bone marrow	1	3.85
Testis + CNS	1	3.85
Total	26	100

Of 26 relapse cases, bone marrow was the major site of relapse, it occurred in 10 (38.5%) cases, followed by CNS and BM + CNS (23.1% and 23.1% respectively).

3.5. Time from relapse to death

Table 5: Time from relapse to death

Status of patient until April 2018	n	%
Alive	7	26.9
dead	19	73.1
Total	26	100
Median time, month range	7.5 ± 8.3	

Comment: Until April, 2018, there was only 7 (26.9%) alive patients, 19 (73.1%) patients passed away. The median time from relapse to death was 7.5 ± 8.3 months

3.6. Relation between relapse events and survival after relapse

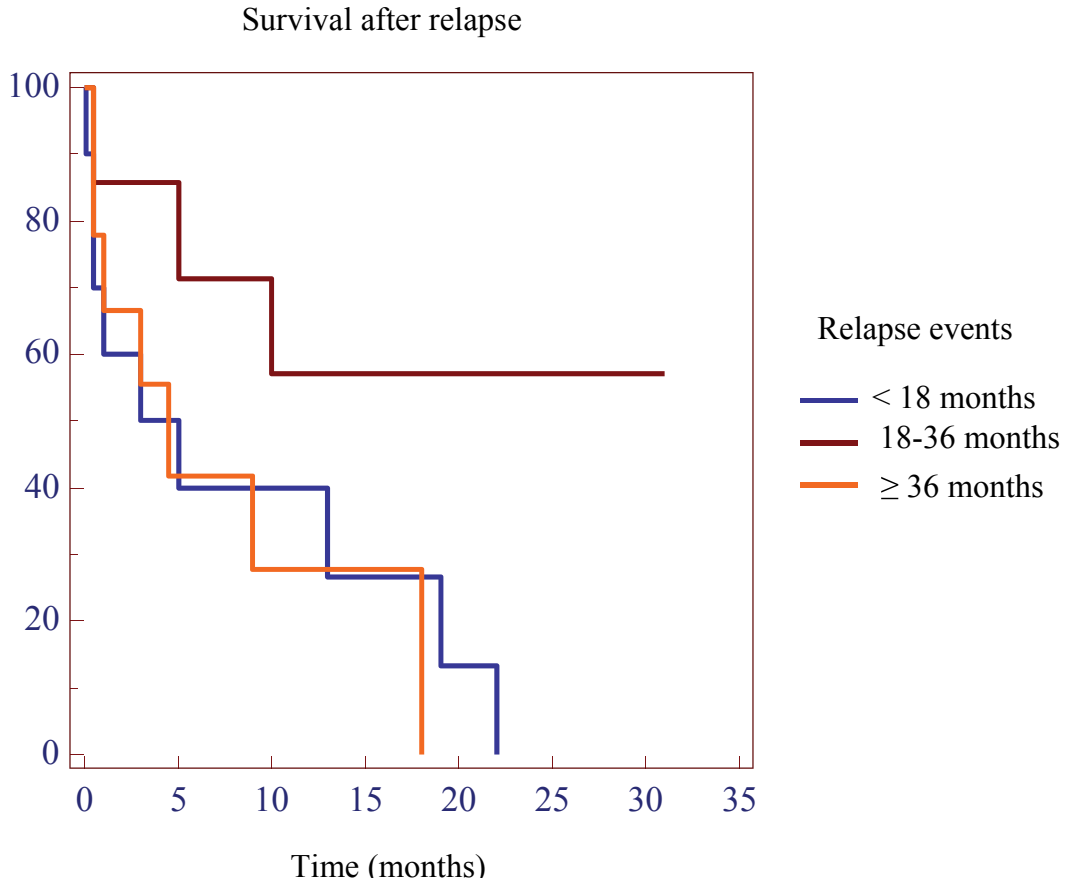

Figure 1: The relation between relapse events and the survival after relapse

Intermediate relapse had better survival time than early relapse

IV. DISCUSSION

4.1. The incidence of relapse rate:

Table 1 showed the relapse rate for ALL was 16.67%. Similarly, Locatelli and Oskarsson showed relapse occurred in 15-20% patients [4], [8]. According to Mulatsih and Nguyen, the rate were higher: 24.5% and 20.5 % respectively [5], [6].

4.2. Characteristics of relapse patients

Table 2 showed the ratio of male to female was 2.7:1. Some researches also showed that the incidence of ALL was higher among boys than girls, and male has a distinctly poor prognosis factor, girls has a better prognosis than boys [9], [10].

High risk group was 1.6 times higher than

standard group (61.5% vs 38.5%) in our study. This result was reasonable, because the high risk group has poor prognosis, with high rate relapse [9]. According to Nguyen, 5 - year survival rates for NCI SR: 50.4 ± 2.4% vs NCI HR: 22.6 ± 2.1% [6].

In our study, of 26 relapsed cases, there were 3 patients (11.5%) didn't achieve remission. This percentage was higher because did the research in small group and we counted the percentage in the relapsed group. Philip showed early response to induction therapy has prognositc value [8].

4.3. Time and site of relapse

The median time from diagnosis to relapse was 28.3± 18.2 months, in which the rate of early, intermediate and late relapse were 38.5%, 26.9% and 34.6% respectively. Based on relapse timing, 53.8% relapsed during maintenance phase, 23.1% relaspe after finishing therapy, 15.4% occurred in delay intensification II phase. Similar to Mulatsih, 59.9% patient relapsed during maintenance phase [5].

Based on their relapse type, bone marrow was the major site of relapse, it reached 38.5%, followed by CNS and bone marrow + CNS (23.1% and 23.1% respectively). The last percentage (15.3%) belonged to testis, testis combined with bone marrow or CNS. According to Mulatsih, the highest site for relapse was bone marrow (67.4%), then the percentage for CNS relapse and testis relapse were the same as our result (19.05% and 13.55% respectively) [5]. Philip A has the same opinion: bone marrow relapse is the principal form of treatment failure in patient with ALL. CNS remains a significant cause of treatment failure in ALL, and the lower percentage for testicular relapse (2-3%) [9]. The reason for relapse testis in our study was higher because or since the testes had long been considered a sanctuary site in the ALL chemotherapy, with high enough doses, the blood-testes barrier can be overcome. And our protocol couldn't be strong enough to eradicate ALL cell in testis [7].

4.4. Time from relapse to death

Table 5 showed the median time from relapse to death was 7.5 ± 8.3 months. Until April 2018, 73.1% of relapsed patient was dead, 26.9% of patients were alive. Our result was lower than other researches. It can be the seasson of our protocol. The protocol wasn't strong enough, and lacking some tests, such as MRD to evaluate the response. According to Gaynon, the median time to isolated BM relapse was about 26 months. The median time to combined relapse was 33 months [1]. According to Nguyen, post-relapsed overall survival rate was higher for patients with isolated CNS relapse (58.7 ± 3.2%) than for patients with either isolated (24.1 ± 2.1%) or concurrent BM (39.4% ± 5.0%) relapses [6].

4.5. Relation between relapse events and survival after relapse

Figure 1 showed intermediate relapse had better survival rate than early relapse. This result was resonable. Time to relapse remains the strongest predictor of survival. According to Nguyen, estimates of 5 year survival rates for isolated bone marrow relapse in early, intermediate and late relapsing patients were 11.5 ± 1.9, 18.4 ± 3.1 and 43.5 ± 5.2% respectively. The relative risk of death for patients with early and intermediate CNS relapses were 3.4 fold and 1.5 fold, respectively, compared with that for patients experiencing late CNS relapses [6]. Van De Berg showed five year EFS rates for early and late relapses were 12% and 35% respectively [11].

V. CONCLUSION

Most relapse cases occurred at maintenance phase and after finishing treatment. Bone marrow and CNS were the main sites of relapse. To tackle these facts, modifying the protocol to use escalated methotrexate dose, and providing further new therapies such as stem cell transplantation need to be applied. With the support from Asian Children Care's League, we are setting up transplantation zone and sending doctors to studying bone marrow

transplantation, we hope in the near future, we can do stem cell transplantation to save relapse children.

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