Long-term outcome of childhood acute myeloid leukemia: A 10-year retrospective cohort study

Tran Kiem Hao, Chau Van Ha, Nguyen Huu Son, Pham Nhu Hiep

Pediatric Center, Hue Central Hospital, Hue, Vietnam

Abstract

Acute Myeloid Leukemia (AML) in children is a serious disease. With a proper treatment, a long-term survival rate above 50% is typical. Before 2010, all the AML patients died in our hospital, and abandonment rate was more than 50%. The aims of this study are to explore the long-term outcome of newly childhood acute myeloid patients treated at Hue Central Hospital from 2010 to 2019.A retrospective study was conducted on 98 children with AML who admitted Hue Central Hospital from January 2010 to December 2019. The diagnosis was confirmed by morphological FAB criteria, cytochemistry and immunophenotype. Patients were treated with using modified AML 7-3 Regimen. Social supports were provided to patients/families. A total of 98 children with AML were analyzed with mean age of 5.6 years ranging from 3 months to 15 years. The male to female ratio was 1.8:1. The overall complete remission rate after induction were 82.6%. Patients accounted for 46 (46.9%) had relapses which occurred in during chemotherapy n=27 (27,6%), after finishing chemotherapy n=19(19,4%). Overall survival at 3 years were 23.2%. The event-free survival at 3 years were 20.2%. Abandonment cases were 4 (4.1%). During the period study, abandonment has been reduced successfully with holistic strategies such as financial support, managing family group, providing education, early follow-up of patients who missed appointments and free accommodation near hospital for patients/families. However, with a high rate patient achieved complete remission after induction phase (82.6%), but the overal survival and event-free survival at 3 years were still low in my hospital (23.2 % and 20.2% respectively). It reflected that it was very difficult to treat successfully AML in low- and middle-income countries. We are considering the way how to improve the quality treatment for childhood acute myeloid leukemia in my hospital.

Introduction

Acute myeloid leukemia (AML) is a clonal disease of the hematopoietic tissue, characterized by abnormal proliferation of myeloid progenitor cells, resulting in insufficient generation of normal mature blood cells.[1] AML accounts for approximately 25% of pediatric leukemia worldwide.[2,3]

The dramatic improvement of outcomes in pediatric AML over the last 3 decades has been achieved with intensification of chemotherapy, improvements in supportive care, wider application of various hematopoietic stem cell transplantations, recent advances in stratification into risk groups based on cytogenetics and more recently on molecular genetics, and early response evaluation by minimal residual disease.[3-5] Currently, the overall survival (OS) in pediatric AML patients ranges from 60-70%.[2,6]

Currently, the likelihood of AML cure in developed countries is around 60%.[1] In Vietnam, treatment for children with AML remains difficult which is carried out in some oncology hospitals. The treatment protocols were not similar among hospitals. The outcome was poor with lots of cases are not received full treatment or even abandonment.

Since 2008, Pediatric Center of Hue Central Hospital applied the protocol AML7-3 for treatment of children with AML. In this study, we report the long-term outcome of childhood AML treated by protocol AML7-3 in our center.

Materials and Methods

From December 2010 to December 2019, ninety-eight newly diagnosed patients with AML under 16 years of age were admitted to Pediatric Center of Hue Central Hospital. The diagnosis of AML were based on morphology, cytochemistry, and immunophenotyping by flow cytometry of bone marrow aspirate and/or peripheral blood, performed with EuroFlow 8-color antibody panels (EuroFlow-ESLHO, Rotterdam, NL) (Table 1). The minimal residual disease was analyzed by flow cytometry in the bone marrow after 21 days of induction treatment. The treatment protocols used were AML7-3 (Table 2).

Medical records were retrospectively reviewed on demographic findings such as age, sex, white blood cell (WBC) count at diagnosis, morphologic, cytogenetic, and molecular classification of AML. Remission induction rate, overall and event-free survival rate, and causes of deaths were analyzed.

Corresponence: Tran Kiem Hao, Pediatric Center, Hue Central Hospital, 16 Lê Lợi, Vĩnh Ninh, Thành phố Huế, Thừa Thiên Huế, Vietnam.
E-mail: trankiemhaobvh@yahoo.com

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Overall survival (OS) was defined as the time between diagnosis and death from any cause or time of last contact. Event-free survival (EFS) was calculated from the date of diagnosis to last follow-up or first event (failure to achieve remission, relapse, second malignancy or death due to any cause, whichever occurred first). Continuous variables were expressed as mean±standard deviation; categorical variables were expressed as numbers and percentages. Probabilities of survival were estimated using the Kaplan-Meier method. P-value <0.05 was considered statistically significant. The software package SPSS version 21.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 98 childhood acute myeloid patients were diagnosed for 10 years (2010-2019). Patient characteristics of children with AML by study periods are shown

in Table 3. Sixty-three patients (64.3%) were males (male/female ratio, 1.8:1). The mean age at diagnosis was 5.56 years (range, 3 mo to 15 yr). Age distribution was: £1 years, 11.2%; 2–9 years, 63.3%; and ≥10 years, 25.5%. A half of cases come from Thua Thien Hue and Quang Tri province. The mean WBC count at diagnosis was 47.24 ± 90.69 (×10⁹/L). The most common subtype as per the FAB classification was AML M2.

At the end of the first cycle, there were 62.2% patients achieved a complete remission, 13.5% had a partial response, and 13.5% were resistant. For those who did not achieve remission, we continued to provide chemotherapy. Of those in partial remission or resistant after the induction phase achieved a complete remission with a subsequent therapy was 20 cases (76.9%). Thus, a total of 82.6% achieved a complete remission. There were 11.2% pattients passed away during the first cycle. There were 27.6% relapsed during chemotherapy, 19.4% relapsed after finish treatment. There were 4.1% patients refused treatment (Table 4). The 3-year OS and EFS rate for the whole cohort were 23.2% and 20.2%, respectively (Figures 1 and 2).

Discussion

Like in other studies, male sex was slightly predominant, and most patients were older than 2 years (Table 3).[7] The most prevalent morphological type was FAB M2 (42.9%), which was in close agreement with previous studies.[7,8] The FAB morphological classification for AML can define treatment and risk group stratification. Chromosomal abnormalities in AML include aberrations described as gain or loss of whole chromosomes structural abnormalities or balanced translocations. The literature reports that the translocation t(8;21) is the most prevalent, varying between 12% and 23% whereas t(15;17) is observed in 3.4-10% of cases.[9,10] According to Sandahl JD, abnormal karyotypes were present in 452 cases (76%) and numerical aberrations were present in 40% (n = 237) of all pediatric AML.[11]

In this study, the 3-year OS and EFS were 23.2% and 20.2%, respectively, for 2010-2019 (Figures 1 and 2). This rate was lower than that of developed countries such as Japan (75%),[2] Europe (69%)[12] and the United States (64%),[6] and lower compared with that of developing countries in Asia, such as China (7-yr OS, 33%)[13] and Thailand (5-yr OS, 35%)[14] (although the study periods and follow-up durations were slightly different among these studies). These disparities may be caused by multiple

Table 1. AML immunophenotyping.

	CD13	CD33	CD34	CD15	CD45	CD14	CD41
M0	+	+	+++	-	+	-	-
M1	+	+	+	-/+	+	-	-
M2	+	+	+/-	+++	+	-	-
M3	+	+	-/+	+++	+	-	-
M4	+	+	-/+	+	+	+	-
M5	+	+/-	+	+	+	+++	-
M6	-/+	+/-	+	-	-	-	-
M7	-	+/-	+	-	-	-	+++

Table 2. Four periods of AML7-3 protocol.

Induction	Intensification 1	Intensification 2	Intensification 3
Cytarabin 100 mg/m²/ day ×7days Daunorubicin 45 mg/m²/ dayx3days. BMA at day 21. If the patient does not achieve remission: - Blast cells > 20%: Cytarabine: 2000 mg/m²/12 hours × 6 days. - 5% < Blast cells <20%: Repeat cytarabine and daunorubicine as above	Cytarabine 1000mg/ m²/12 hours × 4 days -Daunorubicine 45mg/ m² × 3 days	Cytarabine 2000mg/ m²/12 hoursx 4 days Etoposide 100/m² × 4 days.	Repeat intensification 1 or Cytarabine 3000mg/ m²/12 hour × 3 days.

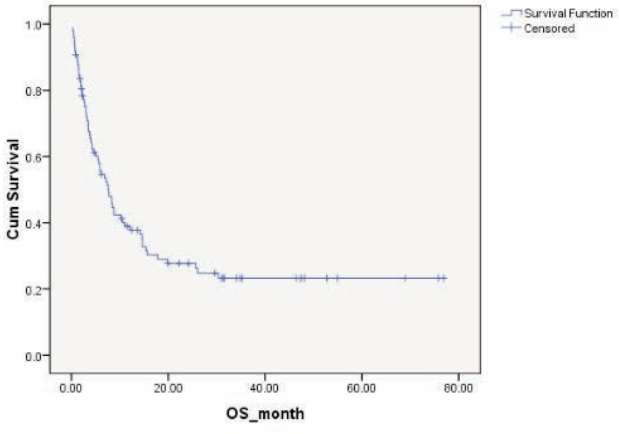

Figure 1. Overall survival curve.

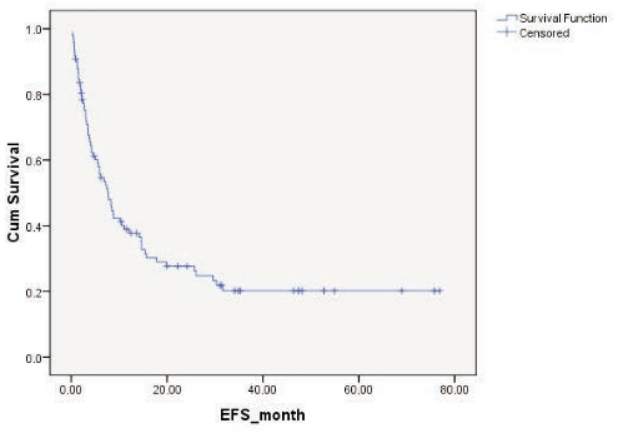

Figure 2. Even free survival curve

factors, with the country's economic status being one contributor. With economic growth, children are more likely to have access to health insurance and to receive a timely diagnosis, high quality treatment, and supportive care, and parents are more likely to adhere to therapy, all of which contribute to improved survival rate of children with AML.[15] These things were true for my patients. Hemorrhagic, and infectious complications were also mainly causing of TRM (treatment related mortality). Sometime platelets and antibitotic, and antifungal were not enough or available in my center.

In the study of Jastaniah W,[16] a total of 193 children diagnosed with de novo AML between January 2005 and December 2012 were identified, of those 175 were evaluable for outcome. The overall survival was 58.8±4% and event-free survival 40.9±4.1%. Xu XJ *et al.*[13] report the outcome of childhood AML treated with modified National Protocol of Childhood Leukemia in China 1997 in a institution from 1997 to 2005. One hundred and eighty-five children with newly diagnosed AML were admitted. The 7-year overall survival and event free survival rates for the whole cohort were 33.1±4.1% and 31.2±3.7%, respectively. Sixty patients (32.4%) refused chemotherapy and 123 were eligible for protocol evaluation. Among eligible patients, 111 (90.2%) achieved complete remission. The estimated 7-year OS and EFS rates were 50.2±5.5% and 46.±5.1%, respectively. Acute promyelocytic leukemia (APL) was more curable than non-APL (7-year EFS: 63.5±7.9% *vs*. 35.9±6.3%, P=0.005). Thirty-one patients (25.2%) relapsed, but no central nervous system leukemia was observed.

The best way to achieve a better outcome for childhood AML treatment is to improve compliance to treatment through an effective comprehensive program that includes: (a) parental education; (b) family affective management; (c) a patient tracking system; and, (d) social services for families (*i.e.*, transportation, food and lodging subsidies). To meet international standards and improve treatment outcomes, we have completely applied the protocols AML7-3 for childhood AML.

The incidence of treatment abandonment has been reduced to 4.1% in the current study. This was obtained thanks to a strong intervention by Asian Children's Care League, which was able to classify the living conditions of patients at the time of diagnosis and to provide support, including a family food bag, money for travel, housing for parents, and other support as needed, together with a program for parents' education to improve their understanding of the disease, special care needs, administration of oral chemotherapy, etc. This result can be regarded as an exceptional achievement and compares favorably with other contemporary experiences.[17,18]

The overall results from this study suggests that intensive therapy can be delivered

Table 3. Demographic characteristics of childhood acute myeloid leukemia by study period.

Variables	ll case (n=98)
Sex	
Male	63 (64.3%)
Female	35 (35.7%)
Mean age (range)	5.56 ± 3.19 (3 months – 15 years)
Age, N (%)	
≤ 1	11 (11.2)
2-5	39 (39.8)
5-9	23 (23.5)
> 9	25 (25.5)
Geography	
Thua Thien Hue	28
Quang Tri	20
Other province	50
Peripheral Blood	
RBC (×10^{12}/L)	3.27 ± 0.63
Reticulocyte	0.24 ± 0.13
Hemoglobin (g/L)	85.12 ± 14.11
WBC (× 10^9/L)	47.24 ± 90.69
Platelet count (x 10^9/L)	65.25 ± 70.20
Blast (×10^9/L)	39.23 ± 39.19
Bone Marrow	
Nuclear cells (× 10^9/L)	121.92 ± 64.94
% Blast	66.20 ± 21.39
Blast cell (× 10^9/L)	80.69 ± 39.19
Abnormal Karyotyp (n=25) (%)	
Hypodiploidy	7 (7.2)
Trisomy 21	5 (5.1)
Hyperdiploidy	13 (13.2)
FAB classification (%)	
M_0	4 (4.1)
M_1	21 (21.4)
M_2	42 (42.9)
M_3	0 (0)
M_4	8 (8.1)
M_5	16 (16.3)
M_6	5 (5.1)
M_7	2 (2.1)

Table 4. Treatment response.

Variables	Number	Percentage
Treatment outcome		
Complete remission	61	62.2
Partial remission	13	13.3
No remission	13	13.3
Death	11	11.2
After subsequent therapy		
Achieve a complete remission	20	76.9
No remission	6	23.1
Relapse (n=46)		
During chemotherapy	27	27.6
After finishing chemotherapy	19	19.4
Abandonment	4	4.1

in a well organized center in an low□middle–income countries and that treatment abandonment can be reduced to a very low incidence with promising results. However, these results remain suboptimal because of the socioeconomic conditions that are associated with a higher risk of late diagnosis and early death. Longer follow-up also is needed to determine whether a plateau at 5 years has been reached with this therapy. Further improvement in survival should be pursued through educational programs to facilitate earlier diagnosis, better management of infectious complications, better knowledge of the disease, and possibly different treatment strategies.

Conclusions

Abandonment has been reduced successfully with holistic strategies such as financial support, managing family group, providing education, early follow-up of patients who missed appointments and free accommodation near hospital for patients/families.

With our efforts to providing less toxic modified protocol to reduce the death. However, with a high rate patient achieved complete remission after induction phase (82.6%), but the overall survival and event-free survival at 3 years were still low in my hospital (23.2 % and 20.2% respectively). It reflected that it was very difficult to treat successfully AML in low- and middle-income countries. We are considering the way how to improve the quality treatment for childhood acute myeloid leukemia in my hospital. How to improve supportive care to reduce infection, compose standard protocol for febrile neutropenia, so we could treat infection more effectively and could provide chemotherapy on time. In addition, management of pain and end-of-life care are the essential components of palliative care to support for patients who are not curable.

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