LONG-TERM OUTCOME OF CHILDHOOD ACUTE MYELOID LEUKEMIA AT HUE CENTRAL HOSPITAL

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ABSTRACT

Background: *Hue Central Hospital (HCH) plays a key role intreating Acute Myeloid Leukemia (AML) in the central zone of Vietnam which covers geographically vast areas. Before 2010, all the AML patients died, and abandonment rate was more than 50%.The aims of this study are to determine the outcome of newly diagnosed children with AML treated at HCH from 2010 to 2018.*

Methods: *This is a retrospective review of 98 children with AML admitted from January 2010 to December 2018. 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.*

Results: *A total of 98 children with AML were analyzed with median 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 (CR) rate on day 21 of induction were 62.2%. 46 patients (46.9%) appeared relapse, in which 27 patients had relapse during the time they recured chemotherapy, 19.4% after finishing chemotherapy. Overall survival (OS) at 8 years were 23.2% .The event-free survival (EFS) at 8 years were 20.2%. Abandonment cases were 4 (4.1%).*

Conclusion: *With less toxic modified protocol, survival rate has been improved and treatment related mortality was minimized though high relapse rate is still an issue. 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.*

I. INTRODUCTION

Childhood acute myeloid leukemia (AML) is a very heterogeneous disease that represents only 15–20% of all childhood leukemia, but unfortunately is still responsible for more than half of the deaths from leukemia [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 (HSCT), 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].

AML prognosis improvement has been made possible by disease stratification into risk groups based on cytogenetics, the evaluation of early response to treatment, and the identification of chemotherapy-induction failure. Currently, the likelihood of AML

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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 not received full treatment or even abandonment.

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

II. MATERIALS AND METHODS

From January 2010 to December 2018, 98 newly diagnosed patients with AML under 16 years of age were admitted to Pediatric Center of Hue Central Hospital. The diagnosis was confirmed by morphological FAB criteria, cytochemistry and immunophenotype (table 1). Bone marrow aspiration was analyzed after 21 days of induction treatment. The patients were treated by using modified AML7-3 protocol (table 2). Social supports were provided to patients/families.

Table 1. AML immunophenotyping

	CD13	CD33	CD34	CD15	CD45	CD14	CD41
M_0	+	+	+++	-	+	-	-
M_1	+	+	+	-/+	+	-	-
M_2	+	+	+/-	+++	+	-	-
M_3	+	+	-/+	+++	+	-	-
M_4	+	+	-/+	+	+	+	-
M_5	+	+/-	+	+	+	+++	-
M_6	-/+	+/-	+	-	-	-	-
M_7	-	+/-	+	-	-	-	+++

Table 2. Four periods of AML7-3 protocol

Induction	Intensification 1	Intensification 2	Intensification 3
Cytarabin 100 mg/m^2/ day x7days Daunorubicin 45 mg/m^2/ dayx3days. BMA at day 21.	Cytarabine 1000mg/ m^2/12 hours x 4 days -Daunorubicine 45mg/ m^2 x3 days	Cytarabine 2000mg/ m^2/12 hoursx 4 days Etoposide 100/m^2 x 4 days.	Repeat intensification 1 or Cytarabine 3000mg/ m^2/12 hour x 3 days.

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.

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, which ever 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 (K-M) 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.

III. RESULTS

A total of 98 primary AML patients were observed over the study period. Patient characteristics of children with AML by study periods are shown in Table 1. Sixty-three patients (64.3%) were males (male/female ratio, 1.8:1). The median age at diagnosis was 5.56 years (range, 3 months to 15 year). 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 (x 10^9/L). The most common subtype as per the FAB classification was M2. The treatment response was shown in table 4

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

Variables	All 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 (x 10^{12}/L)	3.27 ± 0.63
Reticulocyte	0.24 ± 0.13
Hb (g/L)	85.12 ± 14.11
WBC (x 10^9/L)	47.24 ± 90.69
Plt (x 10^9/L)	65.25 ± 70.20
Blast (x 10^9/L)	39.23 ± 39.19
Bone Marrow	
Nuclear cells (x 10^9/L)	121.92 ± 64.94
% Blast	66.20 ± 21.39
Blast cell (x 10^9/L)	80.69 ± 39.19
Abnormal Karyotyp (n=25)	**25(25,5%)**
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%)
M3	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 of patient	Percentage
Treatment outcome		
Complete remission	61	62.2%
Partial remission	13	13.3%
No remission	13	13.3%
Death.	11	11.2%
Relapse (n=46)		**47%**
During chemotherapy	27	27.6%
After finishing chemotherapy	19	19.4%
Abandonment	4	4.1%

The 8-year OS and EFS rate for the whole cohort were 23.2% and 20.2%, respectively (figure 1 and 2).

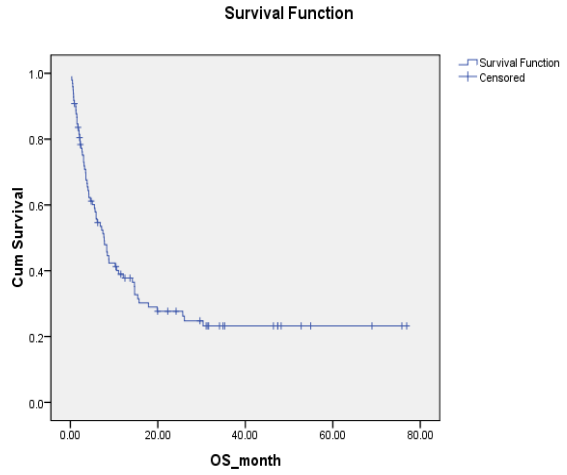

Figure 1. Overall survival curve

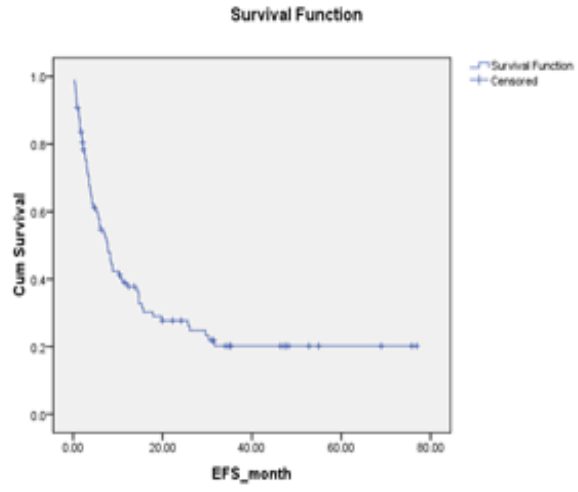

Figure 2. Even free survival curve

IV. DISCUSSION

Similarly in other studies, male 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. In our study abnormal karyotypes were 25 (25.5%), lower than other studies, 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 8-year OS and EFS were 23.2% and 20.2%, respectively, for 2010–2018 (Fig. 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 comparing with that of developing countries in Asia, such as China (7-yr OS, 33%) [13] and Thailand (5-yr OS, 35%) [14].

Our protocol was less toxic, treatment related mortality was minimized however there were high relapsed rate (47%), these patients couldn't be cured because stem cell transplantation is not available in our center. There is the big gap about survival rate between high income and low income countries, these disparities may be caused by multiple 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].

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 (OS) was 58.8±4% and event-

free survival (EFS) 40.9±4.1%. Xu XJ et al [13] report the outcome of childhood AML treated with modified NPCLC-AML97 in a institution from 1997 to 2005. One hundred and eighty-five children with newly diagnosed AML were admitted. The 7-year overall survival (OS) and event free survival (EFS) 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 (CR). The estimated 7-year OS and EFS rates were 50.2±5.5% and 46.9±5.1%, respectively. Thirty-one patients (25.2%) relapsed.

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 safe food, financial support, housing for parents together with a family meeting 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 suggest that intensive therapy can be delivered 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.

V. CONCLUSION

With less toxic modified protocol, survival rate has been improved and treatment related mortality was minimized though high relapse rate is still an issue. The best way to achieve a better outcome for childhood AML treatment is to improve supportive care and stem cell transplantation is needed.

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.

VI. CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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