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Research Article

Outcome of Adolescents and Young Adults with Acute Myeloid Leukemia: A Single-Center Experience

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Abstract
Introduction: *Little is known about the outcomes of Adolescent and young adults (AYAs); aged 15-39 years with acute myeloid leukemia (AML) worldwide, so, we evaluated the clinical characteristics, response to therapy, and survival outcomes of these patients.*
Patients and Methods: *In this observational prospective cohort study, we investigated 64 AYA AML patients, divided by their age at diagnosis into two groups, (AYA 16-29 years) and (AYA 30-39 years); including 26 and 20 patients, respectively. Patient and disease characteristics, in addition to treatment and survival outcomes, were analyzed using statistical package for social science software version 24*
Results: *The median age of the whole group was 29 years, with male-to-female ratio 1.3. The most common FAB subtypes were M2 and M4, 30.4% (for each subtype). Normal karyotyping represented the most frequent cytogenetic risk group (65.2%). An intensive induction therapy was given to most patients (82.6%) and a significant difference was found between the 2 patient groups regarding karyotyping and intensive induction therapy, P-value <0.001 and 0.048, respectively.*
The complete remission rate was (65.2%) and the relapse rate was 40.0% which was significantly higher in the (AYA 16-29 year) group, P<0.001.
The 3-Year leukemia-free survival (LFS) rate was 23.6% and was significantly better within the (AYA 30-39 years) group, p-value = 0.002. While there was no significant difference in overall survival rates.
Conclusion: *AYA patients constitute a unique subset of patients with AML with an improved prognosis especially those aged from 30-39 years, who had better LFS and lower relapse rates.*
Keywords: *Adolescent and young adults (AYAs), acute myeloid leukemia (AML), survival, prognosis.*

Introduction

Over the past 20 years, advances in cancer treatment have significantly improved survival rates for young children and older adults, but these improvements have generally not applied to adolescent and young adult (AYA) group of patients[(1)]. which are generally defined as individuals between 15 to 39 years of age at the time of initial cancer diagnosis[(2)].
The main factors causing these inferior outcomes include a low rate of participation in clinical trials[(3)].
In addition to differences in disease biology, lack of consistency in treatment approaches, poor adherence or intolerance to therapy, delays in diagnosis, and physician's lack of familiarity with cancer in the AYA population[(4)].
AYA patients also face unique developmental and psychosocial issues, which make an adjustment to their disease, health maintenance, and financial hardships more challenging[(5)].
AYA with leukemia represents a unique group of cancer patients that may have distinctive patient and

disease characteristics relative to other age groups and other cancer patients[6]. Much has been reported about the prognosis of AYA with acute lymphoblastic leukemia (ALL)[7].

However, little is known about the therapy and outcomes for AYAs with AML worldwide and more so in low- to middle-income countries[8].

We investigated the clinical characteristics, response to therapy, and survival outcomes of AYA AML patients in order to highlight these patients' prognostic features and to plan for improving their outcomes.

Patients and Methods

In this observational prospective cohort study, all patients with de novo AML (apart from APL) aged from [16 to 39] year-old, treated with induction chemotherapy in Clinical Hematology Unit at Zagazig University from 2017 to 2019 were eligible to be included. Patients aged 16 to 39 years were defined as AYA and are the focus of this analysis [2]. Patient, disease, and treatment characteristics were analyzed, including: age at diagnosis, cytogenetics at time of diagnosis, other disease characteristics, and treatment administered. All patients were treated under protocols approved by the Institutional Review Board, and all patients signed informed consent in accordance with rules and regulations of the Declaration of Helsinki. The study was approved by the Institutional Review Board. A forty-six newly diagnosed AYA patients with AML divided by their age at diagnosis into two group, (AYA 16-29 year) and (AYA 30-39 years); including 26 patients and 20 patients, respectively.

Response Criteria

Response was defined as per the International Working Group criteria[9], we investigated induction mortality, complete remission (CR) and relapse rates, as well as, overall and leukemia-free survival at the end of follow up and patients underwent allogeneic HCT were censored at the time of transplantation.

Statistical Analysis

Kaplan-Meier curves were generated for assessment of OS and LFS with comparison of groups performed by log-rank testing. Fisher exact test or Mann-Whitney U test was employed for comparisons of non-parametric data with categorical or continuous variables, respectively. All tests were two-sided and a p value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS 24 Inc. Chicago, IL, USA).

Results

A total of 46 AYA AML patients, were included in the current study, their median age at diagnosis was 29 years (range, 17-39 years). 20 (43.5%) patients were females and 26 (56.5%) were males, with male-to-female ratio 1.3. Most of them [44 (95.7%) patients] had good PS (0-1), while only 2 (4.3%) patients had poor PS (2-3). The most common FAB subtype was M2 and M4 in the whole group, representing 30.4% (for each subtype) of cases followed by M5, and M1. Normal karyotyping represented the most frequent cytogenetic risk group (65.2% of patients). An intensive induction therapy was given to most patients (82.6%). The median BM Blast % was 70% (range, 28-95). The full clinico-laboratory characteristics of the whole group are listed in Table (1).

When the AYAs were further classified according to age groups, we found that 26 patients had an age range of 16-29 years and 20 patients belong to the 30-39 age group. A significant difference was found between the 2 groups as regard karyotyping and intensive induction therapy, P-value <0.001 and 0.048, respectively. While, no significant difference was found regarding the other baseline characteristics, as in Table (1). After induction chemotherapy, we evaluated the patients for treatment response and we found that 30 (65.2%) patients of the whole group achieved complete remission (CR) and the remaining portion was a refractory disease, while 6 (13.0%) patients died during induction and by the end of the study, a total 24 (52.2%) of patients died. On following up the cases that achieved CR, 12 (40.0%) cases were relapsed, and 12 (26.1%) patients underwent

hematopoietic cell transplantation (HCT) as a consolidation after 1st CR or 2ndCR following salvage chemotherapy, as in Table (2).

On comparing the different age groups as regards the Clinical Outcomes, we found a highly statistically significant relapse rate within the younger group (16-29 ys), P<0.001. While no significant difference with other parameters, Table (2). After a median follow up period of 6.9 (0.8 - 33.2 months), we estimated the survival rates and we found that the 3-Year OS rate of the whole AYA group was 22.2% and the 3-Year LFS rate was 23.6%, Table (3) & Figure (1).

Regarding the survival difference between the patient groups, we detect a significantly better 3-Year LFS within the older (30-39y) age group, with a 100.0% LFS rate and p-value = 0.002. While no significant difference was detected in OS rates, p = 0.272, Table (3) & Figure (2).

Table 1 Clinico-laboratory characteristics of the studied group (N=46)

Parameter		AYA				Total N=46		P-Value
		16-29		**30-39**				
		N=26		N=20				
Age, years		23	17-29	38	30-39	29	17-39	**<0.001**
Sex	Female	12	46.2%	8	40.0%	20	43.5%	0.676
	Male	14	53.8%	12	60.0%	26	56.5%	
Performance Status	0-1	26	100.0%	18	90.0%	44	95.7%	0.099
	2-3	0	0.0%	2	10.0%	2	4.3%	
FAB	M1	6	23.1%	2	10.0%	8	17.4%	0.208
	M2	6	23.1%	8	40.0%	14	30.4%	
	M4	10	38.5%	4	20.0%	14	30.4%	
	M5	4	15.4%	6	30.0%	10	21.7%	
Risk	Fail	2	7.7%	2	10.0%	4	8.7%	0.964
	Fav	2	7.7%	2	10.0%	4	8.7%	
	Intermediate	20	76.9%	14	70.0%	34	73.9%	
	Ufav	2	7.7%	2	10.0%	4	8.7%	
Karyotype	Failure	2	7.7%	0	0.0%	2	4.3%	**<0.001**
	Normal	16	61.5%	14	70.0%	30	65.2%	
	Trisomy	6	23.1%	0	0.0%	6	13.0%	
	Complex	2	7.7%	0	0.0%	2	4.3%	
	DelY	0	0.0%	2	10.0%	2	4.3%	
	t (8;21)	0	0.0%	4	20.0%	4	8.7%	
Intensive induction therapy	N	2	7.7%	6	30.0%	8	17.4%	**0.048**
	Y	24	92.3%	14	70.0%	38	82.6%	
BM Blast %		67	28-95	77	30-93	70	28-95	0.131
PB Blast %		56	25-90	72	0-94	63	0-94	0.322
TLC x10^9/L		19.0	1.3-75	12.0	2.3-72	17.0	1.3-75	0.473
Hemoglobin g/L		7.0	5-11	8.0	4-10	8.0	4-11	0.637
Platelet x10^9/L		30	10-576	35	10-139	34	10-576	0.224

Data expressed by median (range) or n (%) as appropriate,FAB: French-American-British; BM: bone marrow; PB: peripheral blood; TLC, total leucocytic count.

Table 2 Clinical Outcomes the studied group (N=46)

Outcome		AYA				Total N=46		P-Value
		16-29		30-39				
		N=26		N=20				
Death during induction	N	22	84.6%	18	90.0%	40	87.0%	0.591
	Y	4	15.4%	2	10.0%	6	13.0%	
Response	CR	16	61.5%	14	70.0%	30	65.2%	0.550
	NR	10	38.5%	6	30.0%	16	34.8%	
Relapse*	N	4	25.0%	14	100.0%	18	60.0%	**<0.001**
	Y	12	75.0%	0	00.0%	12	40.0%	
Death	N	10	38.5%	12	60.0%	22	47.8%	0.147
	Y	16	61.5%	8	40.0%	24	52.2%	
Underwent HCT	N	22	84.6%	12	60.0%	34	73.9%	0.059
	Y	4	15.4%	8	40.0%	12	26.1%	

Data expressed by median (range) or n (%) as appropriate, HCT: hematopoietic cell transplantation, *relapse calculated among patients who achieved CR.

Table 3: The 3-year overall and Leukemia-Free survival rates in both groups

Group		Total N	N of Events	Censored		Survival Rate %	P
				N	Percent		
3-Year Leukemia-Free Survival Analysis							
AYA	16-29y	(N=26)	12	14	53.8%	00.0%	**0.002**
	30-39y	(N=20)	0	20	100.0%	100.0%	
Overall		(N=46)	12	34	73.9%	23.6%	----
3-Year Overall Survival Analysis							
AYA	16-29y	(N=26)	16	10	38.5%	0.0%	0.272
	30-39y	(N=20)	8	12	60.0%	60.0%	
Overall		(N=46)	24	22	47.8%	22.2%	----

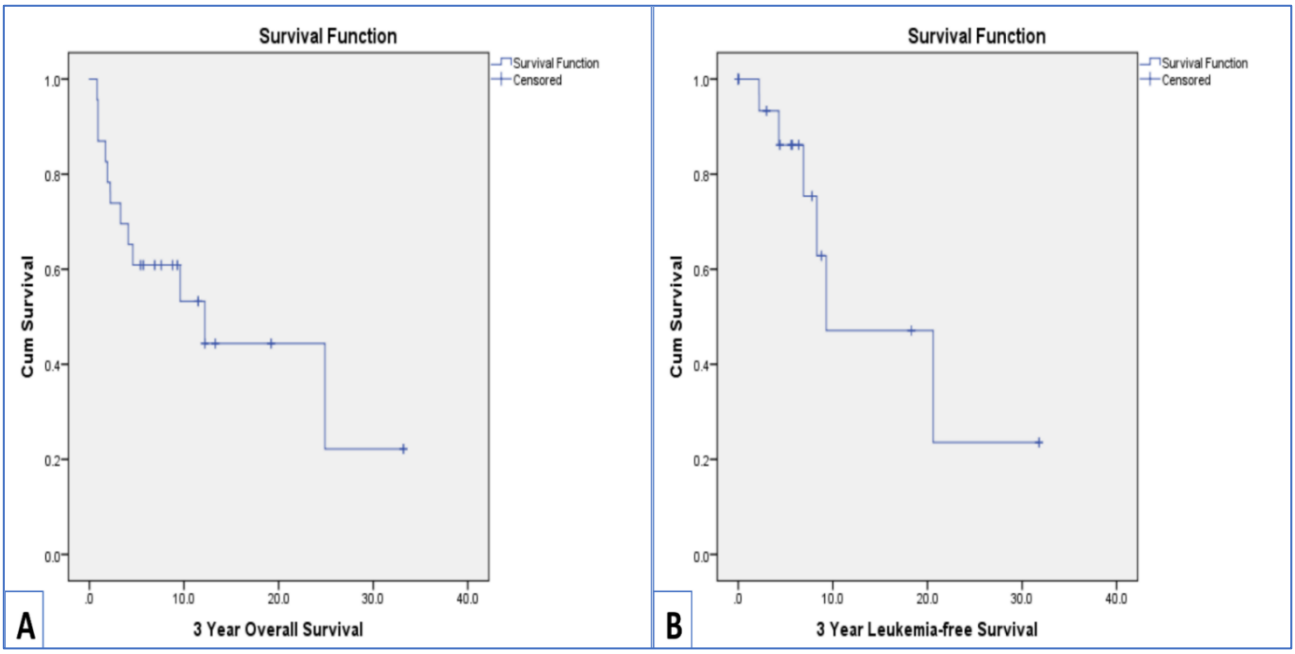

Figure1: The 3-year overall and Leukemia-Free survival rates in all AYA

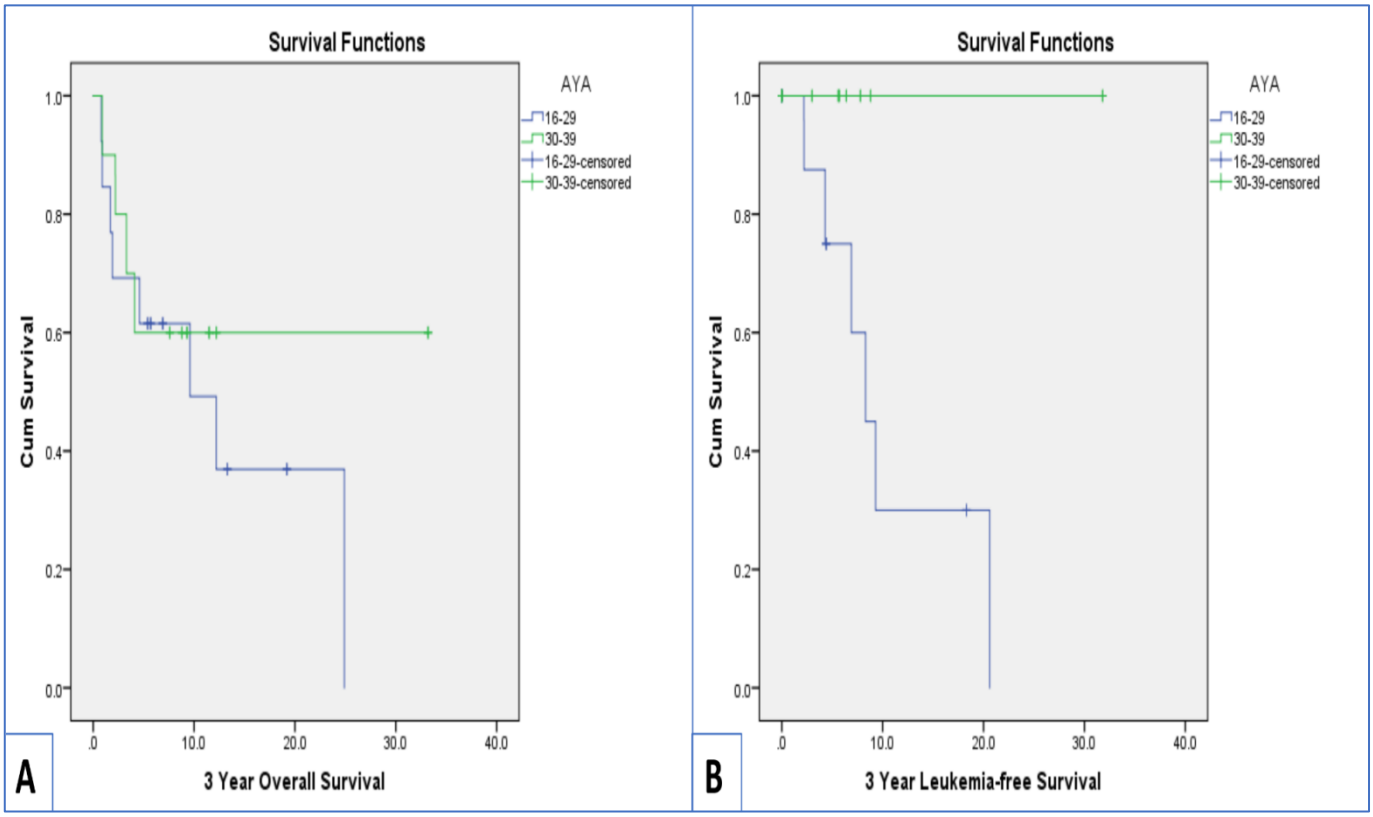

Figure 2: The 3-year overall and Leukemia-Free survival rates in both groups

Discussion

The main finding in this prospective single center study is that, the outcome of AYA patients with AML aged from 30-39 years was significantly better than that aged from 16-29 years, as regards lower relapse rate and better EFS rate. The AYA median age at diagnosis of 29 years with male-to-female ratio 1.3 who were diagnosed as De novo non-M3 AML.

Analysis of the distribution of FAB subtypes showed a predominance of M2 and M4 about 30.4% for both subtypes followed by M5 about 21.7% and 17.4% for M1.Closer results regarding M2 proportion were reported by Jaime-Pérez et al., M2 (30.7%), M4 (23.9%), M5 (21.6%) and 1.1 for M1[8], and also, the American group of pediatric oncology in 2013 reported, M2 (32.5%), M5 (10.8%) and M1 (19.9%)[10], However, among the AYA reported by Housou and coworkers, the distribution of FAB subtypes was dominated by M1 (29.8%), M2 (28.1%) and M5 (9.6%)[11]. The differences in proportions observed, compared to other studies is certainly due to the size of our sample.

The number of patients with an abnormal karyotype was 30.4%, less than the 65% to 80% reported by different leukemia trials[11–13], with intermediate risk category normal cytogenic was the predominant category accounting about 73.9%, this result is closer to other trials that reported normal cytogenetic predominance but with lower frequency from 50-60%[8,11,14]

Complete remission in ours study (65.2%), going with that reported by Housou et. al, and Jaime-Pérez et al., who reported CR rate about (62%) in AYA group[8,11], but is lower than the proportions reported by several groups of studies between 75% and 95% [13,15,16] Refractory disease was found in 34.8% that was higher than that reported by Jaime-Pérez et al, (16.9%) in AYA group. Moreover, Death during induction was only 13% that was lower than Jaime-Pérez et al, (16.9%)[8]. This could be contributed to that all AYA group in that trial received Intensified chemotherapy compared to only (82.6%) in our study. However, patients who underwent HCT were 26.1%, that was comparable to Jaime-Pérez et al, (29.6%) in AYA group[8].

Regarding relapse, was encountered in (40%) of our patients that was lower than reported by other studies (65.9%), possibly due to the difference in follow-up period and inclusion of secondary cases of AML in their trial[8].

The 3-Year Overall Survival for all AYA patients was 22.2% that was different than reported by other studies; 21.3%, 36.4%, 28%, and 47%[11,15,17,18], that's possibly due to inclusion M3 subtypes in their trials which is well known to have better outcome or longer survival estimation for about five years. While, in our study the 3-Year Leukemia-Free Survival for all AYA patients was 23.6%, that was also, a little lower than that reported in other studies, 25.1%, 31% and 33%,[8,11,19].

Upon comparative analysis regarding age groups, most of our patients had good PS 0-1 in both groups, however, AYA from 16-29 received significantly higher intensified chemotherapy than those ≥30 year, that was comparable to other studies with the same age group[8,15]

Also, in our study no significant difference was found between both groups regarding initial laboratory findings like; BM and PB Blast %, TLC $x10^9$/L, hemoglobin g/L and PLT $x10^9$/L. However, AYA patients (16-29) in Pemmaraju and coworkers' study were more likely to have higher TLC, BM and PB blast percent, and higher hemoglobin levels at baseline.

Furthermore, the relapsed disease was higher in our AYA 16-29 while no significant difference was found between both groups regarding CR rates, death during induction, HCT and death between both groups that was similar to data from Jaime-Perez et al., however, the number of those underwent HCT was significantly higher in pediatric group in their trial and no difference in relapse rate in both group, On the contrary, Pemmaraju et al., reported a significantly higher CR rate in AYA (16-29 years), compared to those ≥30 years[8,15]

Regarding survival, AYA ≥30 years, had better 3-Year Leukemia-Free survival in our study, but no significant difference in OS rates, unlike Pemmaraju et al., where AYA 16-29 year carried better EFS and OS, mostly due to the difference in the sample size, follow up and regimen used[15].

Conclusions

Patients with AYA constitute a unique subset of patients with AML with an improved prognosis especially those aged from 30-39 years compared with other age groups who had better event-free survival and lower relapse rates. However, larger multicentre prospective cohort studies are needed before generalization of these findings and to allow adequate characterization of this group of patients.

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