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RESEARCH ARTICLE

Characteristics and Survival of 927 Moroccan Adults with Acute Myeloid Leukemia: Monocentric Experience

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Abstract

Acute myeloïd leukemia (AML) is the most frequent form of acute leukemia among adults and the most aggressive type of leukemia, which is associated with the lowest survival rate. Patients with AML are treated with intensive chemotherapy and many factors could influence the survival of these patients, such as age, cytogenetic abnormalities; white blood cell (WBC) counts. The aim of this work was to study the epidemiological and response profiles of AML adults patients in Morocco. **Patients and Methods:** A prospective, descriptive study conducted in the Hematology and Pediatric Oncology department, 20 August Hospital Casablanca, and concerned adult patients diagnosed with AML through a period of seven years (January 2011 to December 2017). Statistical analysis was performed using SPSS version 20. The overall survival and disease-free survival were evaluated by using the Kaplan–Meier method. **Results:** A total of 927 patients diagnosed with AML during the 7 year period. 466 (50.3%) were males and 461 (49.7%) were females. The median age of patients was 46years. The most represented age group was between 18 and 60 years old with a percentage of 83.2%.The FAB subtype M2 occurred most frequently (27%) followed by M1 (24.8%). The cytogenetic study showed that the majority of patients had a normal karyotype. The t (8; 21) was the most detected balanced translocation in our series and the intermediate cytogenetic group was the most represented group (65.4%). A total of 461 patients (53.54%) were treated according to the protocol AML11. The Disease-free survival (DFS) was significantly better for favorable cytogenetic group as compared to other cytogenetic groups (median survival of 41.58 months for the favorable group versus 29.07 months for the adverse group; p-value = 0.02). **Conclusion:** The age of AML patients was younger compared to other populations. The majority of patients had a normal karyotype and the commonest balanced translocation was the t (8; 21). Survival was higher in patients with good prognosis.

Keywords: Acute myeloid leukemia- Adults- epidemiology- Survival analysis Prognosis

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Introduction

Acute myeloid leukemia (AML) is the most frequent type of acute leukemia among adults and the most aggressive form of leukemia which is associated with the lowest survival rate [1-3]. It is a highly heterogeneous group of hematological disorders that results from the acquisition of chromosomal aberrations and somatic mutations. These abnormalities lead to the accumulation of myeloid precursor cells arrested at early stages of the maturation and differentiation process (myeblasts) [4-5]. In turn, this immature cell accumulation in the bone marrow and blood is responsible for the appearance of insufficiency medullary symptoms such as, anemia, granulocytopenia and thrombocytopenia [6]. The median age of AML at diagnosis (in the late sixties), varied from 63 to 71 years and males are more likely to develop this cancer than females. These results have been reported in developed countries such USA, UK, Canada and Australia [7-12].

AML is a set of diseases with different morphologic, cytochemic, immunophenotypic, cytogenetic, and molecular genetic features. Two classification systems were used to diagnose and classify AML: The first international classification FAB distinguishes eight subtypes of AML based on the morphology of the blast

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cells [13] and the new classification WHO is based on the immunophenotypic, genetic and cytogenetic characteristics [14]. Cytogenetic abnormalities are described in the most of AML types and implicated in the diagnosis; prognosis and therapeutic response that make karyotype an indispensable examination in evaluating this cancer [15-18]. Immunophenotyping is an essential complement to cytogenetic analysis; it allows to refine the diagnosis of AML or even to modify it [19].

Patients with AML are treated by intensive chemotherapy with high-dose cytarabine, anthracycline or by hypomethylating agents (HMA) [20-22]. Many clinical factors influence the survival of AML patients, such as age, cytogenetic abnormalities, secondary leukemia, complete remission after the first induction and white blood cell (WBC) count [23-24]. For the standard treatment with intensive chemotherapy (anthracycline and cytarabine), complete remission was seen (CR) in 60–80% of younger adults. These frequencies have been found in developing countries such as North America and Western Europe [25-27]. However, in developing countries such as Morocco, there is little published informations about the epidemiology and survival of AML patients and there are big differences among AML patients between countries due to socioeconomic, genetic and environmental factors [28].

The aim of the present work was to study the epidemiological, cytologic, cytogenetic characteristics and response profiles of acute myeloid leukemia patients in Morocco.

Materials and Methods

Study type

This was a prospective, descriptive study conducted at the Hematology and Pediatric Oncology department, 20 August Hospital, University Casablanca, and concerned adultpatients diagnosed with AML through a period of seven years from January 2011 to December 2017. The patients were from different regions of Morocco and classified according to the French American British (FAB) classification. The diagnosis of AML was confirmed by the complete blood count (CBC), bone marrow aspiration, Cytogenetic analysis, immunophenotyping and myeloperoxidase cytochemical analysis (MPO). However; molecular biology analysis was not made in all patients.

Cytogenetics

Cytogenetic analysis was made according to standard techniques with RHG banding and the International System for Human Cytogenetic Nomenclature [29]. The patients were divided into three groups according to cytogenetic features: according to the classification proposed by the Southwest Oncology Group [30].

• Favorable risk group: Consisted of patients with inversion of chromosome 16 (inv 16), with translocation t(8;21)(q22;q22) and patients with translocation t(15;17) (q22; q12-21).

• Unfavorable risk group: Consisted of patients with chromosomal abnormalities involving the 5, 7, 17 and 3 chromosomes, patients with Complex karyotypes (three or more cytogenetic abnormalities) and patients with 11q23 aberrations other than t (9;11).

• Intermediate Risk group: Patients with normal karyotypes and patients with Chromosomal Abnormalities that do not fall within the other two groups.

AML-MA 2011 protocol

The chemotherapy treated patients were treated according to the AML-MA 2011 protocol with combined induction chemotherapy using cytarabine (cytosine arabinoside) and daunorubicin. According to this treatment protocol, patients received two inductions of daunorubicin and cytarabine for the first one in addition of etoposide for the second one, followed by three consolidation phases with cytarabine plus daunorubicin for the first and the third phases and asparginase for the second phase. Patients with hyperleukocytosis were treated with hydroxyurea for before induction phase

Inclusion and Exclusion Criteria for Chemotherapy Treatment:

•Inclusion Criteria

Patients with age less than or equal to 60 years who are diagnosed with AML .

Absence of organ dysfunction

• Exclusion criteria

Patients with a confirmed diagnosis aged more than 60 years.

Patients with acute promyelocytic leukemia M3.

Patients with myelodysplastic syndrome (MDS), secondary AML

Remission criteria

After chemotherapy, complete remission (CR) was defined as the absence of circulating blasts, the presence of less than 5% of the blasts in the bone marrow.

Statistical analysis

Statistical analysis was performed with the statistical package for Social Sciences SPSS version 20 (SPSS Inc., Chicago, IL, USA). The values $p<0.05$ are considered to be significant. The analysis of overall survival (OS) and disease-free survival (DFS) of the patients, survival curves were constructed by the Kaplan–Meier method, using the statistical package SPSS version 16 (SPSS Inc., Chicago, IL, USA). The OS was defined as the interval between the date of diagnosis and the date of death or the date of last follow-up. The DFS was defined as the period between the achievement of complete remission (RC) and relapse or date of death from any cause. The curves of OS and DFS were correlated with cytogenetic. Differences in curves were tested using the log-rank test and p-value < 0.05 being considered statistically significant.

Results

A total of 927 patients were diagnosed with AML between January 2011 and December 2017. 466 (50.3%) were males and 461 (49.7%) were females; with a sex ratio of 1.01. The median age of all patients was 46 years with a minimum age of 18 years and a maximum of 90 years. 771 (83.2%) patients were aged from 18-60 (young-adults) and only 156 patients (16.8%) were aged more than 60 years old (elderly). The white blood cell (WBC) count was less than 50 G/L at diagnosis in 71.8% of patients, ranged between 50 G/L and 100 G/L in 13.1% and greater than 100 G/L in 13.3% of patients. The characteristics of the patients are summarized in Table 1. The majority of patients were from the region of Grand Casablanca (41%), 15.6% were from Rabat- sale region and 14.5% were from Tanger-Tetouan region Figure 1.

Regarding the French-American-British (FAB) classification, the M2 subtype was seen in 27% of all patients, followed by M1 (24.8%), and M4 (13.4%) Table1.

85.1% of all patients have benefited from karyotype analysis; the Cytogenetic study revealed that 44% of patients had a normal karyotype, 12% had acomplex karyotype. For the balanced translocations, the t (8; 21) was the most common with a frequency of 8.4%, followed by inv16 (4.7%) and t (15; 17) (3.9%). Trisomy 8 was the most common numerical abnormality in our study (5.3%) Table 2. Concerning the cytogenetic groups, the intermediate cytogenetic group was the most represented group (65.4%), followed by unfavorable cytogenetic group (17.6%) and favorable cytogenetic group (17%)Table 2.

For the annual number of AML patients, the highest annual number was recorded in 2012 (172 cases) and after the 2012 outbreak, the number of AML cases declined Figure 2.

Chemotherapy: 461 patients (53.54%) were treated with cytarabine (cytosine arabinoside) and daunorubicin.

Table 1. Characteristics of Acute Myeloid Leukemia (AML) Cases

		Patients (N=927)
Sex N (%)		
	Females	461(49.7)
	Males	466 (50.3)
M:F ratio		1.01
	Age years (Median)	46
	Range	18-90
	18-30	215 (23.2%)
	31-40	162 (17.5%)
	41-50	186 (20.1%)
	51-60	208 (22.4%)
	61-70	88 (9.5%)
	71-80	55 (5.9%)
	81-90	13 (1.4%)
	Median WBC (G/L) Median	17
	Range	0.15-844
	<50	666 (73.6)
	50_100	119 (13.1)
	>100	120 (13.3)
FAB classification N (%)		
	M0	32 (3.5)
	M1	230 (24.8)
	M2	250 (27)
	M3	52 (5.6)
	M4	124 (13.4)
	M5	46 (5)
	M6	37 (4)
	M7	3 (0.3)
	Not classified	153 (16.5)

Figure1. Map of Morocco Showing the Geographic Distribution of AML Patients

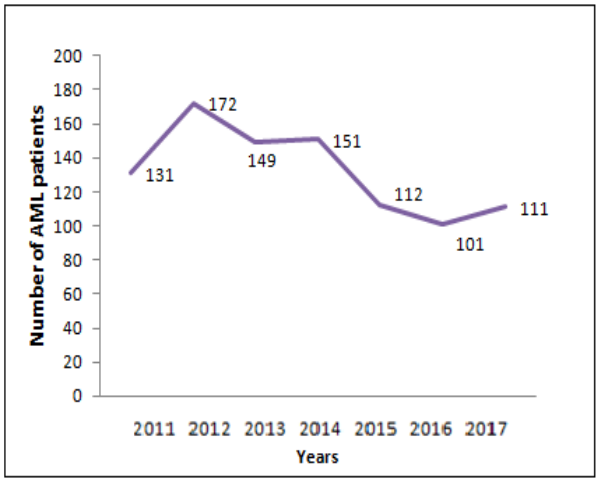

Figure 2. Annual Number of AML Patients

Table 2. Cytogenetic Characteristics of Acute Myeloid Leukemia (AML) cases

Karyotype	Number of patients	%
t (8 ; 21)	66	8,4
t (15 ; 17)	31	3,9
Inv16	37	4,7
Complex	95	12
Trisomy 8	42	5,3
Normal	347	44
Trisomy 21	10	1,3
Trisomy 4	4	0,5
AnyTrisomy	26	3,3
Monosomy 7	21	2,7
Monosomy 5	7	0,9
Monosomy 9	3	0,4
Any Monosomy	26	3,3
Hyperdiploidy	15	1,9
Monosomy X	3	0,4
Monosomy Y	7	0,9
Del 11	19	2,4
Inv2	1	0,1
Inv3	1	0,1
t (3; 3)	1	0,1
t (3,5)	1	0,1
Der1	1	0,1
t (11; 3)	2	0,3
t (2,20)	1	0,1
t (3,18)	1	0,1
t (3,21)	1	0,1
t (5,11)	1	0,1
t (5,16)	1	0,1
t (6,11)	1	0,1
t (7,11)	1	0,1
t (8,16)	1	0,1
t (9,11)	2	0,3
t (9,22)	9	1,1
der 11	1	0,1
t (10,17)	1	0,1
t (11,19)	1	0,1
t (14,15)	1	0,1
Cytogenetic groups		
Favorable	139	17
Intermediaite	134	65,4
Unfavorable	516	17,6
Total	789	100

Survival

The mean overall survival (OS) was 31 months and the mean free survival (LFS) was 20 months. The 5-year EFS and OS Kaplan-Meier estimate were 19.9% and 41.1%, respectively (Figure 3).We compared DFS and

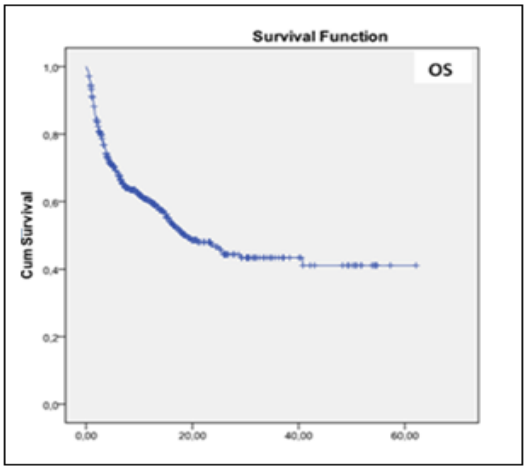

Figure 3. Kaplan-Meier Survival Curves of Overall Survival (OS)

OS between the different cytogenetic groups, the mean DFS differed significantly between different groups (mean survival of 24.5 months for the favorable group versus 14.83 months for the adverse group; p-value = 0.02). The favorable group had longer EFS and OS than other groups and the adverse cytogenetic group was associated with shorter EFS and OS, but, OS did not differ significantly between these cytogenetic groups (mean OS survival of 31.22 months in the favorable group versus 24.72 months in the adverse group; p-value = 0.40) (Figure 4).

Discussion

The median age of our patients was 46 years and the extreme range in age was from 18 years to 90 years. This age was similar to that reported by Bekadja et al in the Algerian population [31]. In contrast, this age was lower than that reported in many other studies, which prove the youthful character of the Moroccan AML patients [7-12-23-32-34]. On the other hand study by Sultan et al in the Pakistan population, reported a median age of 37.5 [35] Table 3.

The age between 18 and 60 years was the most represented age bracket in our series (83.2%). In the study of Padilha et al, patients were predominantly younger than 60 years old (81.6%). Similarly, in the study by Sultan et al 76% of all AML patients (aged between 15-85) were under 50 years old [35-36]. However, according to SEER statistics patients older than age 65 represent approximately 55% of AML cases [37].This disagreement between studies might be explained by the sample size, the recruitment of pediatric patients, differences in demographic characteristics across countries (the pace of population aging, increased life expectancy…..), environmental and genetic factors which could play a crucial role in the appearance of this cancer at a younger age in our AML patients [38-39].The distribution of the population according to sex revealed a slight male predominance; a similar result was reported in most

Table 3. Characteristics of AML Diagnosis in some Populations

Study	The current study (Morocco)	Bekadja et al (Algeria) [31]	Sultan et al (Pakistan) [35]	Wahlin et al (Sweden) [32]	Shyshet al (Canada) [33]	Smith et al (UK) [23]	Phekoo et al (England) [34]
Number of patients	927	1426	125	113	***	717	507
Sex ratio	1.01	1.16	1.5	***	1.25	1.25	1.53
Age years (Median)	46 (18-90)	45 (16-82)	37.5 (15-85)	63 (17-91)	64 (20-64)	68.7	71 (16-98)
Most represented age class	18-60 (83.2%)	***	<50 years (76%)		***	***	≤55 (52.91%)

***, Not available

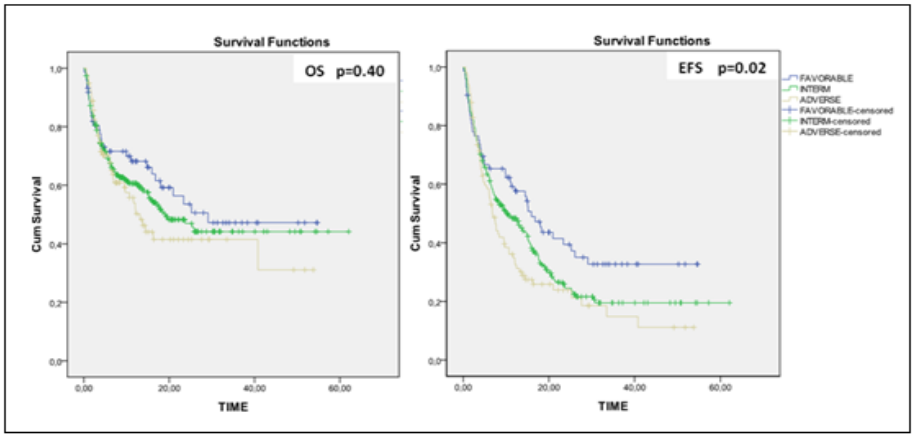

Figure 4. Survival Estimated by Kaplan–Meier Analysis According to Cytogenetic Risk Groups. (A) Overall Survival and (B) Disease-free Survival (DFS)

countries [23-31-33-35-40].

The AML Patients come to the Hematology and Pediatric Oncology department, 20 August Hospital (The closest public hospital to Casablanca) from different regions of Morocco and the majority of them were from the most densely populated region of Morocco, Grand Casablanca with a percentage of 39.4%.

In AML, leukocytosis is a major prognostic factor.In our series, 13.3% of patients had WBC counts higher than 100.000/mm^3. Our results agreed with previous studies by Xu et al., Viana et al., and Imamura et al. who found that the percentage of patients with WBC counts >100,000/mm^3 is between 12% and 15% [41-43].

In this study, M2 was the most common FAB subtype, which confirmed our previous study results [44]. Many other studies also reported that AML-M2 is the most common subtype among both AML adults and pediatric patients [31-45-46]. However, in the studies of Kakepoto et al and Bennett et al, M4 was the most common FAB subtype [47-48] and M5 was found to be the most predominant subtype in the studies of Mertelsmann et al and van der et al [49-50]. These differences could be caused by variations in the genetic background between populations [47].

The karyotype is an essential examination when evaluating AML; chromosomal abnormalities detected on karyotype are one of the most powerful prognostic factors. 44% of patients had a normal karyotype (NK-AML), this result was in agreement with the reported frequency (40-50%) in the literature [51]. The complex karyotype was seen in 12% of all patients, in the literature, AML patients with complex karyotype account for approximately 10–15% of adult AML, wich is in agreement with our result [52-54]. The t (8; 21) was the most common karyotypic abnormalitieswith a frequency of 8.4%, the frequency of this abnormality varied between 5% and 10% of all AML cases and its incidence decreases with age: it's the most common among children and young adults not in patients aged more than 60 years old [55-63]. Other authors obtained similar results [58, 59, 64, 65].

The frequency of t (15; 17) was 4%, a similar result was reported by Khoubila et al in Moroccan young AML population [65]. In our series, the inv16 represents 4.7%, this frequency was similar to that reported in a Tunisian population by Gmiddne et al [66]. Trisomy 8 was the most common numerical abnormality in our study with a frequency of 5.3%, a similar result was found by khoubila et al and this frequency was lower than that reported in Tunisian cohort (7%) [65-65].

The frequencies of prognostic groups in our population were 17% for the favorable group, 65.4% for the intermediate group and 17.6% for the adverse group respectively similar results were reported by other authors [48-67, 68]. However, these results were different to the finding of Khoubila et al in Moroccan young AML population (18 to 60 years), who reported that 19.5% had favorable cytogenetics, 68% had intermediate and 12.5% had poor risk,this difference could be explained by the inclusion of patients aged more than 60 years in our study, the decline in the number of the southern Moroccan AML patients, changes in demographic characteristics of our population [65].

In our series, the annual number of AML patients reduced after the 2012 year, due to the construction of

health facilities such as the built in 2012 of the new public University Hospital (the Mohammed VI) in Marrakech city in which South Moroccan patients receiving their treatment.

The 5-year overall survival (OS) and event-free survival (EFS) rates were 41.1%, 19.9% respectively. Similarly, other authors reported that, the 5-year survival was less than 50% in adult patients younger than 60 and less than 20% in older patients [4, 69, 70].

In a series of 104 Moroccan AML patients treated according to AML 06/96 protocol, the overall survival at 5 years was 9%, these results were insufficient in comparison with the literature [71], compared to this study, there is a big improvement in our results. However, these improvements would be more satisfactory if we can find positive solutions to the major causes of failure seem to be delayed in diagnosis, early (prior to start of therapy) and induction deaths, induction failures and abandonment of therapy.

Cytogenetics play an important role in the treatment and prognosis of AML. In this work, we observed that patients with poor prognosis and intermediate had worse survival from AML and better survival in patients with good prognosis, which showed that Cytogenetics is an important prognostic factor in AML. Similar to results from other studies [34, 72-76].

In conclusion, the age of AML Moroccan patients was younger compared to other populations; M2 was the commonest FAB subtype of AML among our population followed by M1. The majority of our patients had a normal karyotype. Commonest balanced translocation was the t (8; 21). Survival was better in patients with good prognosis. Further national multicenter studies are needed to confirm these results.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' contributions:

- Ait Boujmia Oum Kaltoum : Collected and analyzed the data, Wrote the paper.

- Lamchahab Mouna: provided clinical information, evaluation and advice.

- Nezha Hada: performed karyotyping.

- Quessar Asma: supervised the work, discussed the study results and implications and commented on the manuscript at all stages, correted the paper.

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