

RESEARCH ARTICLE

Characteristics of De Novo Acute Myeloid Leukemia Patients in Palestine: Experience of An-Najah National University Hospital

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Abstract

Objective: To describe the characteristics of de novo acute myeloid leukemia (AML) in the Palestinian population. **Study design and setting:** A retrospective chart review study was conducted at An-Najah National University Hospital (NNUH) during the period of January, 2014 to December, 2016. **Methodology:** The medical records of AML patients treated at NNUH were reviewed. All patients at least 16 years of age diagnosed with de novo AML and started on induction chemotherapy were included. Descriptive statistics were employed to analyze the data. **Results:** Out of 88 patients diagnosed with AML during the study period, 64 had de novo AML and were included. Median age at diagnosis was 36 years, with a male to female ratio of 1.13:1. Two thirds of the cases were from the West Bank and the remainder were from Gaza. Major complaints at presentation were fatigue (64.1%), fever (46.9%), respiratory tract infections (39.1%) and bruising (28.1%). Hepatomegaly was present in 23.4% and splenomegaly in 34.4%. At presentation, the median white blood cells (WBC) count, hemoglobin (Hb) concentration and platelet count were $30.5 \times 10^9/L$, 9.3g/dL, and $39.5 \times 10^9/L$, respectively. According to the French American British (FAB) classification, M4 was the most common subtype (32.8%) followed by M3 (21.9%). After a single cycle of induction chemotherapy complete remission (CR) was seen in 26 (41.9%) and non-remission (NR) in 17 (27.4%), while 19 patients (30.6%) died during the first admission for induction. **Conclusion:** The characteristics of de novo AML in Palestinian patients are comparable to published data elsewhere. M4 was the most common subtype. The outcome of the first cycle of induction chemotherapy was slightly inferior to the published data for M3 patients. Further studies are warranted to identify possible causes.

Keywords: Acute myeloid leukemia- induction chemotherapy- treatment delay- Palestine

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Introduction

Acute Myeloid leukemia (AML) is a subtype of Acute Leukemia caused by the neoplastic proliferation of abnormally differentiated, monoclonal, hematopoietic stem cells in the bone marrow, infiltrating the bone marrow and other organs (Chessells, 2000; Dohner et al., 2015; Hunger and Mullighan, 2015). De novo AML refers to AML in patients with no clinical history of prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents (Cheson et al., 2003). AML is diagnosed when at least 20% of the bone marrow cellularity is blasts (Vardiman et al., 2009). Immunophenotyping using flowcytometry is valuable for the diagnosis and lineage determination of leukemic patients (Lacombe et al., 1997; Döhner et al., 2010). Using the French-American-British (FAB) classification system, AML can be classified based on the morphology and cytochemical properties of the leukemic cells into 8 subtypes; M0 to M7. (Bennett et al., 1976; van der Reijden et al., 1983; Behm, 2003). The initial phase of

AML treatment is induction chemotherapy, which targets the achievement of complete remission (CR). Different protocols are used in the induction treatment depending on the subtype of AML (Estey, 2009; Dohner et al., 2015).

According to the Palestinian health information center, in 2015 leukemia accounted for 8.5% of all cancer cases in Palestine with an incidence rate of 7.8 per 100,000, making it the fourth most common neoplasm in the country. (Palestinian-Health-Information-Center, 2016). Regionally, incidence rates of 8.6 and 6.3 per 100,000 were found in Jew Israelis and Jordanians (respectively (Freedman et al., 2006). The age-adjusted incidence rate of AML in the United States and Europe was 3.4 and 3.7 cases per 100,000 respectively (Ries et al., 2007; Visser et al., 2012; Siegel et al., 2016). Age-wise, AML is usually an elderly population disease, representing about 80% of all elderly leukemia (Visser et al., 2012; Hunger and Mullighan, 2015; Siegel et al., 2016). In previous studies, the clinical presentation of patients, their initial labs and the FAB classification has been variable (Ghosh et al., 2003; Cheng et al., 2009; Salem and Abd El-Aziz, 2012).

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Signs and symptoms of AML are caused by blast cells infiltration of organs. When these cells infiltrate the bone marrow, symptoms of pancytopenia develop. Other organs can be involved, most commonly resulting in enlargement of the liver, spleen and, to a lesser extent, the lymph nodes (Tamamy et al., 2017).

To our knowledge, there are no prior studies addressing the characteristics of AML in Palestine. An adult population (16 or older) with AML diagnosed and treated at An-Najah National University Hospital (NNUH) was targeted. This study aims to describe the characteristics of this population and assess the outcome of induction chemotherapy in de novo AML patients.

Materials and Methods

Study design and settings

This is a retrospective, single-center study conducted at NNUH in Nablus, Palestine. NNUH has an active oncology department accepting on average 800 inpatient admissions each year. It is considered the main referral center for adult leukemia patients from the West Bank and Gaza since January, 2014.

Study subjects

All AML cases admitted to NNUH from January 2014 to December 2016 who were 16 years or older at time of admission, were diagnosed or confirmed to have de novo AML and started on induction chemotherapy at NNUH, were included. Patient with secondary AML and those started on palliative therapy without going through the induction phase were excluded from the study.

Data collection

The files and electronic records of AML patients were reviewed. They include demographic data, detailed history, physical examination and daily progress notes. The lab archives were also reviewed for initial lab results, bone marrow biopsy and flowcytometry results. The data were collected using a predesigned extraction sheet that included all variables of interest. Information was collected from admission until confirmed outcome of

induction was available. The outcome was confirmed by bone marrow biopsy done on days 19-21 after initiation of the induction chemotherapy. The outcome could be either remission (< 5% blasts on bone marrow), non-remission (\geq 5% blasts on bone marrow), or death of the patient during the first admission for the induction chemotherapy.

Ethical issues

Approval for this research was obtained from the Institutional Review Board (IRB) at An-Najah National University. The extraction sheet for each patient was filled anonymously and the data was coded. The collected information was used for research purposes only.

Statistical analysis

Data were inserted into Statistical Package for the Social Sciences (SPSS) statistical software version 23. Analyses of the whole sample were carried out, for M3 vs. non-M3, and Gaza vs. West Bank subgroups. Data were analyzed using descriptive statistics. Each variable of interest was reported as mean \pm standard deviation (SD), median (interquartile ranges IQR) and percentage.

Results

After reviewing all the files of leukemic patients at the oncology department during the study period, a total of 88 patients were found to have AML. Of them, 24 were excluded because their disease was secondary. Sixty-four patients were found to have de novo AML and their full data were extracted. Of these, 53% were males, with male to female (M:F) ratio of 1.13:1. The median age at diagnosis was 36 years with IQR of [25-48.8]. Most of the patients were from the West Bank (65.6%), while 34.4% came from Gaza (see Table1).

The mean duration between the first symptom and admission to NNUH was 33 (\pm 27) days. This duration was 32 (\pm 28) and 34 (\pm 27) for patients from the West Bank and Gaza respectively (see Table1).

Major complaints at presentation were fatigue (64.1%), fever (46.9%), respiratory tract infections (39.1%) and bruising (28.1%). Other complaints were seen in minority

Table 1 Patients' Demographic Data and Duration for Admission and Treatment

Variable number (%)	Diagnosis		Region		Total
	M3	Non-M3	Gaza	West Bank	
Gender 64 (100%)					
Male	4 (29%)	30 (60%)	13(59%)	21 (50%)	34 (53%)
Female	10 (71%)	20 (40%)	9(41%)	21 (50%)	30 (47%)
Age 64(100%)					
Mean in years(\pm SD)	28.5 (\pm 10.0)	40.3 (\pm 15.3)	38.3 (\pm 14.5)	37.4 (\pm 15.6)	37.7 (\pm 15.1)
Median in years[IQR]	26 [21-36]	38 [28-50]	37 [28-50]	36 [24-48]	36 [25-48.75]
Duration between first symptom and admission 61(95%)					
Mean in days(\pm SD)	25 (\pm 23)	35 (\pm 28)	34 (\pm 27)	32 (\pm 28)	33 (\pm 27)
Median in days[IQR]	14 [10-30]	30 [14-40]	30 [14-40]	30 [14-30]	30 [14-40]
Duration between presentation to NNUH and start of induction chemotherapy 61(95%)					
Mean in days(\pm SD)	3 (\pm 3)	5 (\pm 4)	3 (\pm 2)	5 (\pm 4)	4.3 (\pm 3.4)
Median in days[IQR]	2 [1-5]	4 [2-6]	3 [2-4]	4 [2-7]	3 [2-6]

Table 2. Patients' Clinical Presentation and Initial Lab Results

Variable number (%)	Diagnosis		Total
	M3	Non-M3	
Symptoms and signs 64(100%)			
Fatigue	8 (57.1%)	33 (66%)	41 (64.1%)
Fever	2 (14.3%)	28 (56%)	30 (46.9%)
RTI	6 (62.9%)	19 (38%)	25 (39.1%)
Bruising	8 (57.1%)	10 (20%)	18 (28.1%)
Hepatomegaly	2 (14.3%)	13 (26%)	15 (23.4%)
Splenomegaly	3 (21.4%)	19 (38%)	22 (34.4%)
Hepatosplenomegaly	1 (7.1%)	11 (22%)	12 (18.8%)
Lymphadenopathy	2 (14.3%)	7 (14%)	9 (14.1%)
Gingival Hypertrophy	0 (0)	6 (12%)	6 (9.4%)
Weight loss	2 (14.3%)	15 (30%)	17 (26.6%)
Night sweating	1 (7.1%)	16 (32%)	17 (26.6%)
Pallor	2 (14.3%)	8 (16%)	10 (15.6%)
Oral thrush	1 (7.1%)	2 (4%)	3 (4.7%)
UTI	0 (0)	3 (6%)	3 (4.7%)
Skin infections	3 (21.4%)	11 (22%)	14 (21.9%)
Heavy menses	3 (21.4%)	1 (2%)	4 (6.3%)
Epistaxis	0 (0)	6 (12%)	6 (9.4%)
Gum bleeding	4 (28.6%)	4 (8%)	8 (12.5%)
CNS	4 (28.6%)	5 (10%)	9 (14.1%)
DIC	5 (36%)	4 (8%)	9 (14.1%)
Labs			
WBCs count 62(96.9%)			
Mean x10 ⁹ /L(±SD)	49.8 (±127.6)	81.4 (±99.7)	74.3 (±106.3)
Median x10 ⁹ /L[IQR]	10.15[1.5-37.5]	43.4[8.8-109]	30.5[6.2-95]
ANC 49(76.6%)			
Mean x10 ⁹ /L(±SD)	3.2 (±4.9)	13.0 (±22.7)	10.8 (±20.5)
Median x10 ⁹ /L[IQR]	1.0[0.2-4.2]	3.6[1.2-15.7]	2.9[2.9-10.4]
Hb concentration 62(96.9%)			
Mean g/dL(±SD)	9.2 (±2)	9 (±1.9)	10.8 (±20.5)
Median g/dL[IQR]	9.8[7-10]	9.2[8.25-9.95]	9.30[8-10]
Platelets count 62(96.9%)			
Mean x10 ⁹ /L(±SD)	32.5 (±28.4)	80.7 (±109.5)	69.8 (±99.1)
Median x10 ⁹ /L[IQR]	20.5[17-50]	48.5[15-92]	39.5[15-86]

ANC, Absolute Neutrophils Count; CNS, involvement: any clinical evidence of CNS infiltration (e.g. focal neurological deficit, headache, blurred vision, etc.) or documented metastasis on imaging; DIC, Disseminated Intravascular Coagulopathy; Fever, Temperature > 37.5 orally; Hb, Hemoglobin; Heavy menses, menses lasting > 6 days or associated with clots; Hepatomegaly, splenomegaly, Detectable enlargement on physical examination or imaging studies; RTI, Respiratory tract infections, recurrent Upper RTI or Lower RTI or RTI not responding to conventional treatment; Skin infections: any skin or soft tissue infection like cellulitis, erysipelas, abscess, etc; UTI, Urinary tract infection, presence of symptoms suggestive of lower or upper UTI, and confirmed by urine analysis and culture; WBCs, White Blood Cells; Weight loss: unintentional documented loss of > 5% of total body weight in 6 months.

of patients as summarized in Table 2. Hepatomegaly was present in 23.4% of patients and splenomegaly in 34.4%. Other infiltrations were seen in the lymph nodes (14.1%) and the gingiva (9.4%). Disseminated Intravascular

Table 3. Outcome of the First Cycle Induction Chemotherapy

Variable number (%)	Diagnosis		Region		Total
	M3	Non-M3	Gaza	West Bank	
Outcome 62 (96.9%)					
CR	5(35.7%)	21(43.8%)	6(28.6%)	20(48.8%)	26(41.9%)
NR	1(7.1%)	16(33.3%)	6(28.6%)	11(26.8%)	17(27.4%)
Death	8(57.1%)	11(22.9%)	9(42.9%)	10(24.4%)	19(30.6%)

Coagulation (DIC) was present in 9 patients (14%); 5 of which were from the M3 group representing 36% of that group. The other 4 were from the non-M3 group representing 8%.

At presentation, the median White Blood Cells (WBCs) count was 30.5x10⁹/L, with an IQR of [6.2-95] x10⁹/L. The median Absolute Neutrophil Count (ANC) was 2.9 x10⁹/L, with an IQR of [2.9-10.4] x10⁹/L. The median Hemoglobin (Hb) concentration was 9.3g/dL, with an IQR of [8.1-10]g/dL, and the median platelets count was 39.5x10⁹/L, with an IQR of [15-86] x10⁹/L (see Table 2). According to the FAB classification, M3 accounted for 21.9% of all cases. Other non-M3 subtypes comprised 78.1%, which included 3 patients with an unspecified subtype even by flowcytometry. Overall, the most common subtype was the M4 (32.8%) followed by the M3 (21.9%), and the least common was M7 (1.6%) subtype.

Out of the 64 patients who received induction chemotherapy, the outcome of 2 patients could not be tracked because they were referred to other hospitals upon their requests. Of the remaining 62 patients that received their treatment at NNUH, 26 (41.9%) showed complete remission, 17 (27.4%) showed non-remission, while 19 (30.6%) died during the first admission for induction (see Table 3). Eight of the deaths (57.1%) were of the M3 group and 11 (22.9%) of the non-M3 group. Ten (24.4%) of the West Bank patients died compared to 9 (42.9%) of Gaza's. Infection and bleeding were the most common causes of death during the first admission. Septic shock, pneumonia and pulmonary hemorrhage were also frequently reported.

Discussion

This study describes the characteristics of 64 de novo AML cases treated at NNUH, the main referral center for adult leukemic patients in Palestine since January, 2014. Therefore, it represents valuable information about the status of the disease and its outcome in Palestine. The median age at diagnosis for our population was 36 years, which is lower than what has been reported from other studies. Two studies on other Arab populations reported a median age of 37 in Egypt (Salem and Abd El-Aziz, 2012) and 39 in Jordan (Ayesh et al., 2012). A study on a Chinese population reported a median age of 42 years (Cheng et al., 2009). While in the United Kingdom (UK) the median age was much higher (around 70) (Li et al., 2016). It is important to note that the median age remains lower in our study despite excluding the pediatric population, while

this population was included in the studies from Egypt, China and the UK. The median age for M3 patients was lower than non-M3; 26 compared to 38 years, respectively. The same results have been reported from China as well (Cheng et al., 2009). A slight male preponderance was present in our study with a M:F ratio of 1.13:1, which was close to the M:F ratio reported in the study from China (1.2:1) (Cheng et al., 2009). The ratio was higher in Jordan (1.86:1) (Ayesh et al., 2012), Egypt (1.7:1) (Salem and Abd El-Aziz, 2012) and India (2.5:1) (Ghosh et al., 2003). On the other hand, M3 showed female preponderance, with M:F ratio of 1:2.45. Cheng et al reported that the M:F ratio in M3 patients from China was 1.2:1 (Cheng et al., 2009).

Patients with AML are usually symptomatic but the clinical manifestations are heterogeneous. Patients often have symptoms of Red Blood cells (RBCs), WBCs or platelet dysfunction. Our patients had fatigue (64.1%), fever (46.9%), respiratory tract infections (39.1%) and bruising (28.1%) as the major manifestation at presentation. These results were similar to other studies; for example, Salem and Abd El-Aziz reported that pallor (63%) and fever (41%) were the most common clinical features in Egyptian AML patients (Salem and Abd El-Aziz, 2012). Similar results were reported from Iraq, with symptoms of anemia and fever being the most common (64% and 51% respectively) (Naji, 2014). Indian patients had close presentation, with pallor and fatigue being the most common presenting manifestations (82%) (Ghosh et al., 2003).

In this study, splenomegaly was reported in 34.4% which was similar to what was reported from other studies on Arab Egyptian and Iraqi patients (34% in both) (Salem and Abd El-Aziz, 2012; Naji, 2014). However, the results were higher than what was reported in Indian patients (20%) (Ghosh et al., 2003). Hepatomegaly was seen in 23.4% which is slightly higher than what was reported from Iraq (21%) (Naji, 2014) but lower than the results from Egypt (43%) (Salem and Abd El-Aziz, 2012). Lymphadenopathy, which is not often seen in AML patients, was present in 14.1%. This is slightly less than what was reported from Egypt and Iraq (19% in both) (Salem and Abd El-Aziz, 2012; Naji, 2014) and much less than what was reported from India (36%) (Ghosh et al., 2003).

The mean duration between the first symptom perceived by the patient and admission to NNUH in this study (33 ± 27 days) was close to what was reported from Iraq (32 ± 22 days) (Naji, 2014). It was noted that this duration was shorter in M3 (25 ± 23 days) compared to non-M3 (35 ± 28 days) patients. This shows that M3 patients have a more acute and dramatic presentation (Lee et al., 1994).

At presentation, the median WBCs count was $30.5 \times 10^9/L$, this is higher than what was described in Egypt (median $13.2 \times 10^9/L$) (Salem and Abd El-Aziz, 2012) and Iraq (median $10 \times 10^9/L$) (Naji, 2014). In the M3 group, the median WBC count was $10.15 \times 10^9/L$ which was lower than that for non-M3 patients ($43.4 \times 10^9/L$). Similar results were described in India (Ghosh et al., 2003). The median Hb at diagnosis was 9.30 g/dL,

while in Egypt a median of 8.4 g/dL was reported (Salem and Abd El-Aziz, 2012). The median platelet count was $39.5 \times 10^9/L$. While in Egypt the median platelet count was much higher at $62 \times 10^9/L$ (Salem and Abd El-Aziz, 2012). A wide range of Hb (4.0-13.8)g/dL and platelet ($(1-650) \times 10^9/L$) counts were found in this study, which could be explained by the fact that some patients received blood-product transfusion before admission to NNUH while others did not, therefore these were not included as prognostic indicators.

The most common subtype from the FAB classification in our study was M4 (32.8%). Similar results were reported from Egypt, with M4/M5 accounting for 34.5% of their patients (Salem and Abd El-Aziz, 2012). On the contrary, M4 was the least common subtype in China (5.4%) (Cheng et al., 2009), and among the least common in Iraq (2%) (Naji, 2014). In Jordan the most common subtype was M5 (Ayesh et al., 2012). The M3 subtype was the second most common after M4 in our study accounting for 21.9% of our cases, which is comparable to what was reported from Egypt (23%) (Salem and Abd El-Aziz, 2012). M3 was the second most common in Jordan as well (Ayesh et al., 2012).

M2 was the most common subtype in the Indian (32%) and Iraqi (49%) studies (Ghosh et al., 2003; Naji, 2014). However, in our study, the M2 subtype represented only 12%. The differences in the subtypes between regions support the assumption that there is geographic heterogeneity in AML, which could be attributed to the genetic composition of the population or other environmental factors (Ghosh et al., 2003; Enjeti et al., 2004; Cheng et al., 2009; Salem and Abd El-Aziz, 2012; Thuler and Pombo-de-Oliveira, 2016).

The time from admission until treatment (treatment delay) was shorter in the M3 group compared to the non-M3 with means of 3 (± 3) days and 5 (± 4) days respectively. This was the case in Brazil as well (Thuler and Pombo-de-Oliveira, 2016). These results suggest that M3 is recognized and treated earlier than other subtypes due to its fatal outcome. Overall, treatment delay in our study was shorter than what was reported from Brazil (Thuler and Pombo-de-Oliveira, 2016), indicating a rapid diagnosis and treatment.

Regarding outcome of induction chemotherapy, 42% of patients had complete remission (CR) after a single cycle of induction chemotherapy, this is slightly lower than what Naji (2014), Holowiecki et al., (2004) and Cassileth et al., (1998) reported in their studies (47%, 47% and 56% respectively) (Cassileth et al., 1998; Holowiecki et al., 2004; Naji, 2014). Other single center studies focused on the outcome after treatment regardless of the number of courses of induction chemotherapy. Such studies showed huge variation in CR rates from 23.7% to 70% (Alymara et al., 2004; Strasser-Weippl et al., 2012). Nineteen patients (30.6%) died in our study before discharge from the first admission. This is lower than what was reported from Brazil (46.1%) (Thuler and Pombo-de-Oliveira, 2016), but higher than what was reported by Holowiecki et al., (2004) (15.5%) (Holowiecki et al., 2004). In our study, the outcome of different subtypes was close to other studies, except for the M3 group in which our CR rate of 35.7 %

was slightly inferior to that reported by others. Tellman et al reported a much higher CR rate of 72% (Tellman et al., 1997). This lower CR rate for M3 patients in NNUH is despite them presenting earlier than other subtypes and being on treatment more promptly. This poor outcome can be partly explained by the higher rates of DIC in this group, but other studies could not identify DIC as a poor prognostic factor (Shahmarvand et al., 2017). Therefore further studies are required to determine the exact cause and improve patient care.

Strengths and Limitations

This study is the first study on the clinical profile of de novo AML patients in Palestine. Therefore, it represents a strong foundation for further studies on this disease. It also sheds light on some differences in the outcomes between NNUH and other centers worldwide, which warrants more research in this aspect to identify possible causes that could lead to changes aiming to improve health care. The small sample size has precluded the use of inferential statistics. The retrospective nature of the study and its dependence on archives are could limit the accuracy of the data. In order to ascertain the correctness of data, we reviewed every piece of information carefully, compared between lab charts, electronic data and written progress notes. We also fulfilled the checklist provided by the STROBE statement (STrengthening the Reporting of OBServational studies in Epidemiology) in order to improve the quality of this study. It is a challenge to compare between different populations due to limited population based studies and most of the studies being center-based (Cheng et al., 2009). Additionally, there was some heterogeneity in reporting data, for example, some studies included pediatric population while others did not, and this made comparison much more difficult.

In conclusion, this study reports the characteristics of de novo AML patients in Palestine. In most aspects, our results are comparable to regional published data M4 was the most common subtype. The outcome of the first cycle of induction chemotherapy for M3 is slightly inferior to the published data; this requires further research to identify the causes and improve quality of care.

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