RESEARCH PAPER

Overview of Iraqi experience in management of acute promyelocytic leukemia

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Abstract

Objectives: In Iraq, leukemia is the 4th most common cancer, and acute promyelocytic leukemia contributes to 2.83% and 3.18% of leukemia in Iraqi males and females respectively. The aim of this study is to review the presentation and management outcome of patients with acute promyelocytic leukemia in Iraq.

Methods: A hospital-based cross-sectional study was conducted over the period of 15 months in different hematology centers. A total of 58 patients with acute promyelocytic leukemia were enrolled in this study (53 newly diagnosed and 5 relapsed cases). Diagnosis was based on morphology with or without cytogenetic study.

Results: The mean age was 33.1±13.8 years, with slight female predominance. Most cases presented at winter season (39.7%). Sanz severity scoring classification of patients as (25.9%) with low risk, (53.4%) intermediate risk, and (20.6%) high risk disease. Induction protocol consist of chemotherapy plus ATRA in (58%), while (36.2%) received only ATRA plus ATO. At the end of induction, (86.2%) of patients had complete remission, while only 13.8% had failure of induction and death. Induction mortality was higher in those who had received chemotherapy-based regimens. At relapse, a second complete remission had been achieved in 4 out of 5 cases (80%).

Conclusion: There is a predilection of acute promyelocytic leukemia to young age group and winter season presentation. The choice of non-chemotherapy regimens, especially for the low and intermediate risk group, showed no drawback in complete remission rate. Disease outcome in Iraq has improved over several years due to increasing experience with using different regimen.

Keywords: Acute promyelocytic leukemia, ATRA, Arsenic Trioxide, Chemotherapy, Iraq

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Introduction

Acute promyelocytic leukemia (APL) is a rare disease, comprising around 5–10% of AMLs of the adult, with an estimated incidence of 0.1/100000 in Western countries [1].

In Iraq, APL contributes to 0.84 % of all leukemia cases. It constitutes 2.83%, and 3.18% of leukemias in Iraqi males and females respectively, according to the annual report of Iraqi cancer registry 2018.

The characteristic cytogenetics translocation t(15;17) was found in most of the cases with the resultant abnormal fusion between promyelocytic leukemia gene and retinoic acid receptor (PML/RARA) [1] that results in a malignant cell [2]. Classical cases show strong positivity for CD33, expression of CD13 and CD117, infrequent expression of HLA-DR and CD34, and lack of CD11a, CD11b and CD14 [1].

In 1985, all-trans retinoic acid (ATRA) had made a big change in managing APL. Adding ATRA to chemotherapy, up to 90-95% were able to achieve complete remission (CR). [3]

Since1990s, the use of arsenic trioxide (ATO) had added more to the outcome of newly diagnosed as well as relapsed refractory APL. [3]

It is worthy to say that as a result of 40 years of clinical trials, the most fatal subtype of AML, the APL, is being considered now as the most curable.[4]

The stratification of APL risk according to Sanz stratification based on WBC and platelet counts remains the most reliable and validated way to rapidly identify high-risk APL patients. [5]

Sanz et al defined patients with WBC ≤10 000/μl and platelet count > 40000/μl as low risk, WBC ≤10 000/μl and platelet count ≤40000/μl as intermediate risk and WBC >10000/μl as high risk.[6]

Low-risk disease is better treated with less intensive regimens than those patients presenting with high-risk disease.[7]

The combination of ATO plus ATRA was used as first line management at least in the low/intermediate risk group [8, 9] as compared with ATRA plus chemotherapy, this regimen is equally effective if not better, and it carries more treatable side effects.[10]

For high risk patients, it is recommended to use ATRA plus anthracycline-based chemotherapy [11] with a CR of more than 90 %. The early death of APL is the main cause of treatment failure, caused mostly by CNS bleeding.[12]

Those patients who receive induction by chemotherapy free approaches, the recommended consolidation is by 4 courses of ATO and 7 courses of ATRA. While patients who received induction by conventional ATRA/ chemotherapy approach, consolidation will be a 2-3 courses of anthracycline based chemotherapy.[11]

Till now, cytarabine in consolidation, at a high or intermediate dose, given in at least one cycle, for high-risk patient <60 years, will decrease the risk of relapse, but no change in overall survival (OS) [11]

A maintenance regimen of ATRA, 6-mercaptopurine (6-MP) and methotrexate (MTX) for 2 years had adopted for all patient according to routine guidelines to get less relapse rate on high-risk patient (APL 2000 and APL 93). [13]

The new recommendation for patients treated with chemotherapy-free approaches is not to use maintenance [11.]

This study aims to review of APL course in terms of patient characters, presentation, risk stratification, and different management approaches, as well as the treatment related complications and outcomes in Iraq.

Methods

Study settings and design

A hospital-based case series study was conducted in different hematology centers in Baghdad, including Baghdad Teaching Hospital hematology center and the private nursing hospital in the Medical City Complex, hematology department in Al-Imamian Al-Kadhimain medical city, and the National Center of Hematology/ Al-Mustansiriya University throughout the period from July 2018 till September 2019, i.e., 15 months duration.

All patients were informed about the research, their consent were taken for participation.

Selection of study subjects

It includes all patients (15 years or more) who were diagnosed with APL based on morphology

(by complete blood count (CBC), blood film, bone marrow aspirate and biopsy), with or without suggestive Flow cytometry and, whenever possible, with genetic confirmation by presence of t(15,17) or PML/RARA by RT-PCR.

Data collection

Through direct interviewing of patients and reviewing their file registry, the demographic data of APL Iraqi patients were collected. All cases were confirmed by reviewing the laboratory investigations: CBC, blood film, bone marrow aspirate and biopsy, flow cytometry, and cytogenetics.

Patients were followed throughout the study period in order to assess the outcome by phone contact using social media technology.

Definitions of outcome

Complete remission (CR): The disappearance of all disease features in response to treatment. It is based on the following criteria: the disappearance of abnormal promyelocytes on bone marrow aspirate, normalization of coagulation and fibrinolysis parameters, a neutrophil count of greater than 1,500/µL, a platelet count greater than 100,000/µL, and no transfusion requirement.

Overall survival (OS): The length of time from either the date of diagnosis or the start of treatment for a disease, till death in weeks

Treatment failure: Resistant to treatment or death from any cause.

Statistical Analysis

Data were analyzed using statistical package for the social sciences (SPSS version 23) computer software program. Analytic statistics as Student t test used to find association between categorical variables and continuous variables, and fisher exact test to find association between two categorical variables. Survival analysis was done by log rank and overall survival by Kaplan-Meier test for one year duration. The p-value less than or equal to 0.05 was considered to be statistically significant.

Results

Demographic data

A total of 58 APL patients were enrolled in this study. The mean age was 33.1±13.8 years. The disease was more predominant in females, with a male to female ratio of 1:1.4. Most of the patients, 23 (39.7%), were first presented at winter. (Table 1)

Table 1: Demographic data of all patients

Variables	Description	No.	%
Age at diagnosis (years)	<20 years	13	22.4
	20-29 years	14	24.1
	30-39 years	11	19
	40-49 years	11	19
	≥50 years	9	15.5
	Mean ±SD (Range)	33.1±13.8 (5-62)	
Gender	Male	28	48.3
	Female	30	51.7
Residence	Baghdad	38	65.5
	Other	20	34.5
Seasonal of presentation	Winter (December-February)	23	39.7
	Spring (March-May)	15	25.9
	Summer (June-August)	10	17.2
	Autumn (September-November)	10	17.2

Clinical presentations:

Majority of the patients (79%) were suffering from coagulopathy at time of presentations in form of bleeding, apart from 3 patients who suffered from thrombosis. Organomegally, including gum hypertrophy, was seen in only (5.2%) of patients. (Figure 1).

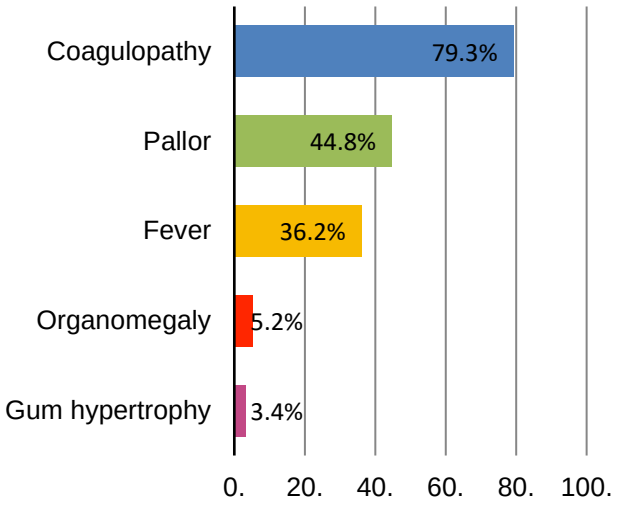

Figure 1: Distribution of Clinical Presentations

Hematological parameters:

Pancytopenia was the presenting manifestation in 41% of patients. All patients had been diagnosed on morphological basis by having malignant promyelocytes in peripheral blood and/or bone marrow, while only (25.9%) of patients had flow cytometry for diagnosis, and (37.9%) had cytogenetically proved disease. (Table 2)

Risk stratification

Based on Sanz score categories, 20.6% were labeled as high risk, unlike intermediate and low risk groups that constituted (53.4%), (25.9%) respectively. A classical APL morphology was described in (82%).

Treatment strategy:

Induction protocols

Unfortunately, two patients had passed shortly after receiving ATRA alone. One more patient had received ATRA alone and refused neither taking chemotherapy nor ATO. In the remaining 55 patients, ATRA (in a dose of 45 mg /m^2) was either combined with ATO (36.2%) in a dose of 0.15 mg/kg, or more commonly combined with chemotherapy (58.6%) like doxorubicin in a dose of 30 mg/m^2, given in 4 doses at days 2, 4, 6 and 8 from starting ATRA. Induction duration ranges between 30-39 days in (32.6%), between 40-49 days in 10.3% of cases, between 50-59 days in 22.4%, and ≥60 days duration in only 5.2%.

Table 2 : Hematological parameters at presentation and diagnostic methods

Test	Parameters	Mean ±SD	Range
CBC	WBC(x103/µl)	10.95±19.81	(0.30-124)
	Haemoglobin (g/dl)	8.34±1.96	(4.6-13.5)
	Platelets (x103/µl)	36.97±31.55	(7.1-205)
Blood film	Malignant Promyelocytes %	33.76±34.95	(0-96)
BM study	Malignant Promyeloctes%	62.95±30.05	(5-95)
Coagulation study	PT (sec)	16.33±5.62	(11.2-39)
	PTT (sec)	32.13±6.54	(20-59.6)
Methods used for diagnosis		No.	%
Morphology	Blood film and/ or BM study	58	100
Immune phenotyping	Flowcytometry	15	25.9
Genetic	Cytogenetic or molecular	22	37.9

SD, standard deviation; CBC, complete blood count; WBC, white blood cell count; PT, prothrombin time; aPTT, activated partial thromboplastin time; BM, bone marrow

Induction outcome

CR was achieved in 86.2% (50) of patients; while the rest, 13.8% (8), had died due to bleeding,

infection, or differentiation syndrome. The most frequent complications of induction were neutropenic fever and differentiation syndrome (Figure 2)

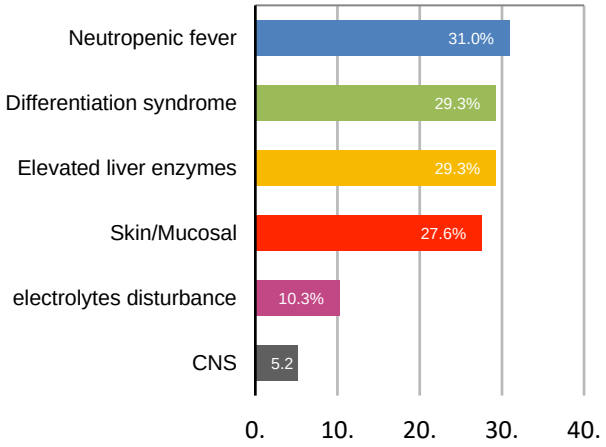

Figure 2 : Complications during induction

Consolidation protocols

Only 44 patients with CR had received consolidation courses, as 6 patients had not received consolidation for different reasons (lost to follow up, referral, refusal of treatment).

They were either combinations of ATRA + ATO (61.3%), or ATRA plus chemotherapy in (38.7%). During consolidation, one patient had died because of sepsis.

Maintenance course:

Only (34) patients had finished consolidation courses whereas 53% (18) had kept on maintenance but the other 47% (16) had stopped treatment with no maintenance.

Outcome interpretation

The mean age in patients who had failure of induction therapy due to death was 37.8 years while the mean age in patients who had complete remission (CR) was 32.3 years with no significant difference between age of patients and induction outcome (p= 0.29).

There was no significant association between gender, and the induction outcome (p= 0.25, 0). (Table 3)

Table 3: Relation of demographic data of studied group with induction outcome

Variables	Description	Induction outcome		P value
		Death	CR	
Age at diagnosis (years)	Mean age	37.8	32.3	0.29*
Gender	Male	2(7.1%)	26(92.9%)	0.25**
	Female	6(20%)	24(80%)	
Residence	Baghdad	5(13.2)	33(86.8%)	0.56**
	Other	3(15%)	17(85%)	

CR, complete remission . *Student T test ** fisher exact test , significant ≤0.05.

The mean WBC count was higher in those with failure of induction therapy due to death (24.1 $x10^3$/ml) compared with achievement CR outcome (8.4 $x10^3$/ml) which is of statistical significance (p=0.038).

The mean hemoglobin level was lower in case of induction failure (6.5 g/dl) than that for CR group (8.5 g/dl) which is also significant (p= 0.006).

There was no significant difference in relation to platelets count with induction outcome (p= 0.16), and similarly concerning malignant promyelocytes percentage in blood film and bone morrow and coagulation study with induction outcome (p>0.05). (Table 4)

High risk stratification had an impact on failure of induction therapy secondary to death in 33.3%, with a significant association between risk stratification and induction outcome (p= 0.04). There was no statistically significant association between classical morphology or variant APL form with early induction outcome (p= 0.61).

The protocol of induction has influenced the induction outcome; but with no statistical significance (p= 0.38). Only 4.5% of patients with ATRA+ATO had failure of induction, in comparison to 15.1% of those who had received ATRA+chemotherapy.

The duration of induction was statistically associated with induction outcome (p= 0.006), as shorter than 30 days of induction had attributed with failure outcome in 35.3% unlike those with longer ≥ 30 days duration of induction. (Table 5)

Table 4: Relation of Hematological parameters with induction outcome

Test	Mean value	Induction outcome		P value
		Death No.	CR No.	
CBC	WBC (x103/µl)	24.1	8.4	0.038 *
	Haemoglobin (g/dl)	6.5	8.5	0.006 *
	Platelets (x103/µl)	22.7	39.7	0.16*
Blood film	Malignant Promyelocytes %	32.5	33.9	0.91*
BM study	Malignant Promyeloctes%	47.5	66.2	0.12*
Coagulation study	PT (sec)	17.5	55.3	0.75*
	PTT (sec)	33.2	32	0.702 *

CR, complete remission
***Student T test, significant ≤0.05.**

Kaplan Meier analysis has showed that the 1-year overall survival was 84.5% (at end time for data collection, nine patients were still within consolidation courses and not completing one year from time of diagnosis). (Figure 3)

Table 5: Relation of Induction protocols and duration with induction outcome

Protocol	Induction outcome		P value
	Death	CR	
ATRA + ATO	1(4.5%)	21(95.5%)	0.38*
ATRA + chemotherapy	5(15.1%)	28(84.4%)	

CR, complete remission; ATRA, all trans retinoic acid; ATO, arscenic trioxide
***fisher exact test , significant ≤0.05.**

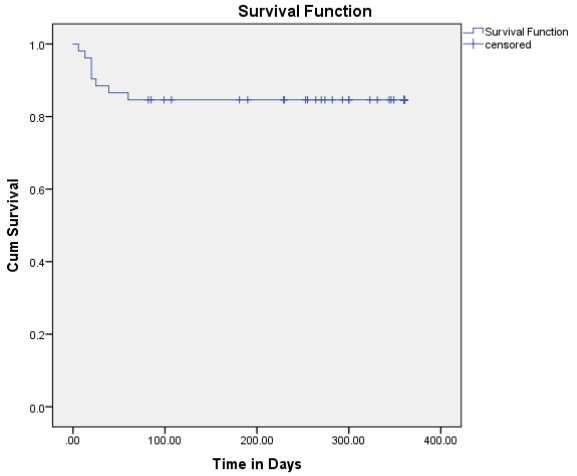

Figure 3: Kaplan Meier survival analysis for 1-year overall survival

Survival distributions for the different levels of risk stratification had showed that, the mean survival in high risk was the lowest (204 days) while the highest was found in low risk (300 days) with significant difference in survival distributions (p= 0.035). (Figure 4)

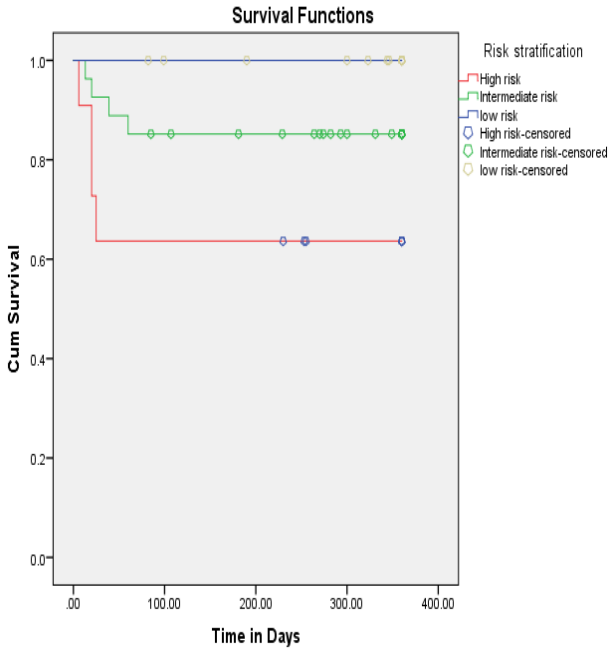

Figure 4: Survival analysis according to risk stratifications

Discussion

APL in general is a disease of young age group, and this was true for the current study, as the mean age was 33.1 years, which is in agreement to other Iraqi studies; Al-Shemari et al. 2005,[14] and Ahmed, et al. 2018.[15] The female gender slightly dominates, which was also seen in Pakistan APL patients (Sadia Sultan et al, 2015) with a male to female ratio of 1.2:2 [16] but in contrary with Al-Shemari et al. 2005, [14] Ahmed, et al. 2018, [15] and Cunningham et al. 1989 [17] .

There is a seasonal predilection for APL manifestation, as more than one third of the cases were diagnosed during Winter (December-February). This seasonality preference is also shown in a US study about seasonality in all AML subtypes, that the months of AML case diagnosis in which annual peaks in the overall count were observed during December and January, Calip et al. 2013.[18] A similar predilection is also shown to be true with APL in a study done in Brazil, which concluded that the correlations found between rainfall and number of cases of APL could be related to the dispersion of pollutants into the environment, Barroso KS et al. 2013.[19] An other explanation is by immunity changes over different seasons, as proposed by Randy J. Nelson, and Gregory E. Demas, , Nelson RJ et al 1996.[20]

Bleeding tendency is a common presentation, which is similar to Al-Shemari et al. 2005, [14] Khorshid O et al 2011,[21] and Bajpai et al 2007,[22] reprts. Thrombosis was an initial presentation in 5.1% of cases, which is in agreement with Ahmed, et al. 2018 Chang et al., 2013; and Mitrovic et al., 2015. [15]

The incidence of thrombosis in APL is higher than in other subtypes of acute myeloid leukemia and risk of thrombosis has been associated with elevated WBC count and presence of FLT3-internal tandem duplication (Breen et al., 2012). [16]

Based on the risk score, about half of patients were of an intermediate risk while the least common category was the high risk. In similarity, Bajpai et al 2007 [22] and in the larger GIMEMA and PETHEMA trials (Sanz et al., 2000). [16]

At the end of induction course; about 86.2% of patients have complete remission which is a higher induction CR than that of Al-Shemari et al. 2005 (73%) [14] Ahmed et al 2018 (68%) [15] and Cunningham et al 1989 (75%).[17] This clearly improving CR rate, may reflect the increasing

awareness, better supportive care, availability and early initiation of ATRA in our hematology centers.

In most of cases of death, there was more than one cause, the highest attribution was for infection and hemorrhage. This is higher than that of Ahmed et al 2018, in which the main cause was also infection (36%), followed by bleeding (28%), as other causes were unrelated to the disease due to long duration of follow up. [15]

The protocol of induction had play a role on outcome although it was of non-statistical significance (p=0.38) but this is in agreement with what has been concluded from the Phase III trial that randomized standard risk patients with APL to treatment with ATRA/chemotherapy vs. ATRA/ATO. In which the results showed non-inferiority of ATRA/ATO regimen compared to ATRA/chemotherapy, Lo-Coco et al 2013.[23]

It is found that the longer the duration of induction, the higher rate of CR, (p=0.006). This may be because most of death cases had occurred early in the induction course, the time in which the risk of coagulopathy is greater.

The one-year overall survival was 84.5%, which is very much higher than that of Al-Shimary et al. 2005(66%) [14] while it was 37.8%, 78%, 82% in Ahmed et al 2018, [15] Cunningham et al 1989 [17]. This increasing OS reflects the success in APL management following the use of higher ATRA doses 45mg/m^2, and the introduction of ATO in most of Iraqi hematology centers.

Conclusion:

there is predilection to young patient disease, with more seasonal variation in presentation. Throughout the time an improving experiences and orientation with rapid diagnosis, risk stratification management as well as good supportive care can had achieved an appreciable early CR. Any combination of induction and consolidation chemotherapy can provide good long-term outcome but the use of non chemotharpy regimen may be advised for many instances with no drawback on the outcome. Longer duration for induction would give more deeper and durable response.

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Conflict of interest: The authors declare no conflict of interest.

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