All Trans Retinoic Acid (ATRA) therapy in acute promyelocytic leukemia AML-M3
Results of treatment of 29 Iraqi adult patients with AML-M3

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Background: All trans Retinoic acid (ATRA) when combined with chemotherapy induce complete remission in more than 85% of cases of AML-M_3 , and significantly increase overall survival (OS) and Leukemia Free Survival (LFS).

Aim of the study: to evaluate the efficacy of ATRA therapy in low dose (25mg/m^2) together with anthracyclin-based regimen in achieving (Complete Remission) CR in patients with AML-M3.

Patients and methods: Twenty nine patients with newly diagnosed AML-M3 (acute promyelocytic leukemia) based on morphology according to FAB (French-American-British) association enrolled between December2003 to June 2006. For induction of remission with ATRA therapy in dose of 25 mg/m^2/day in two divided doses for 4-6 weeks along with anthracyclin-based chemotherapy and closely monitored clinically and laboratory to evaluate the response and to look for the complications . Mean follow up duration was 108 weeks.

Results: Twenty nine patients with mean age of 43 year. Twenty three patients were cases of classical AML-M3 (79%) and 6 were cases of variant subtype (21%). Sixteen patients (55%) were males while 13 (45%) patients were females, Twenty one patients (73%) achieved complete remission, with induction related mortality of 27% (8 patients of 29). Three died because of ATRA syndrome, three due to sepsis and the other two because of intracranial hemorrhage, Three patients of those who achieved complete remission (CR) eventually relapsed, two within the first year of CR and died because of their disease, while the third one relapsed after one year of CR and achieved a second remission, After a median follow of 108 weeks the DFS was 86% and the OS 66%. Nine patients developed ATRA syndrome which proved to be fatal in three of them.

Conclusion: ATRA therapy in a dose of 25 mg/m^2/day in two divided doses with anthracyclin-based chemotherapy achieved CR in the majority of newly diagnosed adult Iraqi patients with AML-M_3.

Key words: AML-M_3, ATRA

Introduction:

Acute Promyelocytic leukemia (AML-M3) is distinct subtype of Acute Myeloblastic leukemia (AML) representing 8-10 % of all AML[1,2]. It is characterized, Clinically by coagulation disorder that can result in early death caused by bleeding in lungs or brain and Cytogenetically by chromosomal translocation (15:17)[1]. As early as 1988 investigators in Shanghai reported that treatment with ATRA in 24 patients resulted in partial remission (PR) or complete remission (CR)[3].

In contrast to chemotherapy, ATRA (vitamin A derivative) cause no bone marrow hypoplasia but promotes the differentiation of the leukemic cells [3].

A recent update Kaplan- Meier trial at 4 years showed that event free survival and relapse rate were significantly better (*P*=0.0001 for both) among patients who received both ATRA and chemotherapy than among those with chemotherapy-alone arm. At 4 years, 78% of chemotherapy-alone patients had relapsed, compared with only 31% of patients who received both ATRA and chemotherapy [4].

The evolution of Management of APL [5]

At 1967, different trials of chemotherapy treatment were unsuccessful to achieve CR. Later on between 1973 &1988, better outcome had achieved with use of anthracyclins in the presence of good control of the associated coagulopathy (CR of 50-80%).

When ATRA therapy had introduced between 1988 &2001 in combination of intensive chemotherapy, the results improved to reach about ≥70 % cure rate [6].

Over the last decade a new agent used which arsenic trioxide (ATO), either alone or in combination with ATRA. It is approved for the management of relapsed/ refractory APL [6].

The ATRA syndrome (RAS):

It is the commonest treatment complication, and defined as acute differentiation syndrome resulting in capillary leakage. It has been reported at any time within few days after initiation of ATRA therapy with a median of seven days [7].

No specific pre- treatment factor (including the WBC count) is significantly associated with occurrence of RAS[8]. Although hyperleukocytosis is frequently observed prior to ATRA syndrome, this reaction may occur with normal WBC count in up to one third of cases [8]. In the absence of biological

criteria of ATRA syndrome the diagnosis was entirely based on clinical feature according to the definition by Frank et al by collection of[9]:

I -Definitely present; when all the following symptoms and signs present which are fever, dyspnea, pleural and/or pericardial effusion , pulmonary infiltrates, weight gain .Hypotension was also included by many other studies.

II-Indeterminate; when 2-4 of the above symptoms and signs were present.

III- Definitely absent in the remainders.

Patients and methods

Eligibility:

Twenty nine patients with mean age of 43 year , were followed in this study between December 2003 till June 2006 in the Hematology ward of Baghdad teaching hospital .

After have been diagnosed as a case of Acute Promyelocytic leukemia (AML-M_3) according to French-American-British (FAB) classification.[10]

Unfortunately neither chromosomal study to confirm the characteristics finding of t (15, 17) nor molecular study to confirm PML- RARα gene or protein available and we did not exclude patients with initial poor performance status, nor those initially presented with significant complication like initial presentation with CNS involvement.

Induction Therapy:

The patient received ATRA therapy at a dose of 25mg/m^2/ day in two divided doses P.O until achieving remission (for6-8weeks) with Anthracyclin-based regimen therapy. [11]

Maintenance Therapy:

6- Mercaptopurine ` (50mg/m^2) per oral daily with Methotrexate (15-20mg/m^2) per oral or by intramuscular weekly injection with ATRA pulse therapy every three months when available.

Definition of outcome:

Complete remission (CR) and relapse were defined according to the National Cancer Institute criteria &similarly the toxic effects were graded according to the common toxicity criteria of the National cancer Institute. Three years survival (OS) calculated from the time of starting induction till death in weeks. Three years disease free survival (DFS) was defined as the time from the beginning of (CR) to relapse, or death from any cause. Failure was defined as resistant leukemia or death from any cause.

Early death: death occurring during induction therapy or during the period of aplasia after chemotherapy.

Statistical Analysis:

SPSS v.10 had used for statistical assessment. The patients' characteristic, response, evaluation, toxicity assessment were presented by descriptive statistical methods. Survival and disease free survival were described using the Kaplan- Meier method. *P* value of $\leq$ 0.05 was an indicator of statistically significant difference.

RESULTS

1. The patients' characteristics:

Twenty nine patients with mean age of 43 years were included in the study group.

Sixteen of them (55%) were male.

The majority of them presented initially with active bleeding (82%). (Table 1)

Table -1- the demographic characteristics of the study group

Patients' characteristic		No.	%
Sex:	Male	16	55
	Female	13	45
Age:	<60 years	26	89
	>60 years	3	11
Symptomatic bleeding		24	82
Lymphadenopathy		2	6
Organomegally (splenomegally)		3	11
WBC count:	$\leq 5x10^9$/l	19	66
	$> 5x10^9$/l	10	24
Platelets count < 50 x 10^9/l		29	100
Morphology:	Classic type	23	79
	Variant type	6	21

2. Complications:
Eight patients out of the 29 patients enrolled in the study were died during induction phase; three had died because of sepsis, three because of ATRA syndrome while the cause of death of the other two patients was intracranial hemorrhage. The adverse effects experienced during ATRA therapy were generally well tolerated a part from ATRA syndrome (Table 2)

Table-2- The adverse effects associated with ATRA therapy during the period of remission induction

ADVESE EFFECTS*	No.	GRADE 2	GRADE 3-4
Weight gain	20/29	20	0
Blood pressure alteration:			
Increase	23/29	17	5
Decrease	2/29	2	0
No change	4/29	-	-
Hyperglycemia	14/29	10	4
Serositis ± effusion	10/29	6	4
Cardiac impairment	3/29	2	1
Pulmonary manifestation	14/29	8	6
Renal impairment	14/29	12	2
Thrombosis	3/29	2	1
Periosteal reaction	5/29	3	2
Psychological (aggression)	2/29	1	1
Decrease visual acuity	2/29	1	1
Dermatological	2/29	1	1
ATRA syndrome	8/29	2	6
Definite	4	-	-
Indeterminate	4	-	-

* According to national cancer institute criteria

3. Outcome:
Twenty-one patients (73%) achieved CR within 30 days of ATRA therapy .Three patients (14%) relapsed later on; two within the first year and died with their disease, while the other patient relapsed after 18 months and achieved 2nd durable remission, The three years DFS of the study group was 86%. (Table 3)

Table -3- the outcome of the study group.

Outcome	No	%
Death during induction of remission	8	27
Complete remission(CR)	21	73
Relapse	3	14
3 year DFS	18/21	86
Overall survival (OS)	19/29	66

P value≤0.001

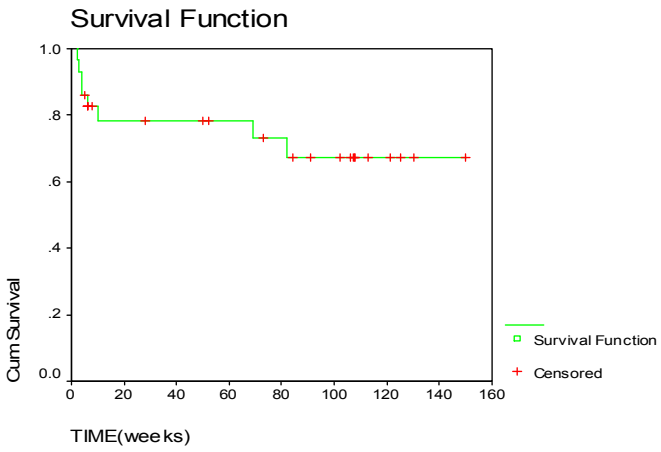

Figure -1-: Overall survival (OS) of study group (Kaplan – Meire)

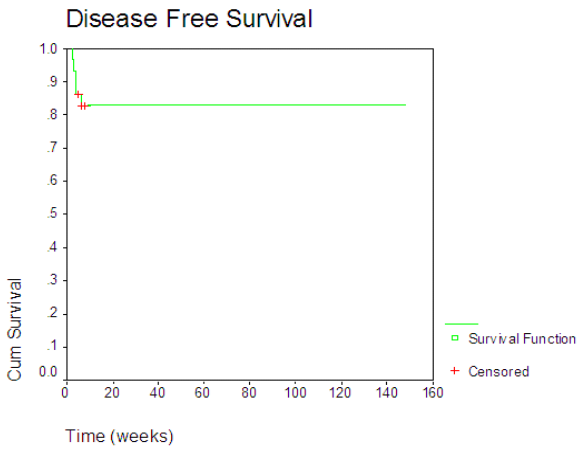

Figure -2-: Disease Free Survival (DFS) of the study group (Kaplan – Meire) ($p \leq 0.0001$)

Comparison with the results of other studies

THE STUDY	CR%	Induction mortality%	OS%	DFS%	Relapse %	ATRA Synd. %
MRC adult leukemia working party study;120 patients	87	13	71	72	20	25
PETHEMA group ; 123 patients	89	11	82±4	79±4	6±11	26
European APL 93-96 group; 96 patients	92	8	82	84	11	15
Memorial Sloan-Kettering Cancer Center ; 51 patients	86	14	78	85	14	49
Baghdad Teaching Hospital; 29 patients (Present study)	73	27	66	86	15	27

Discussion:

Before the era of ATRA, acute promyelocytic leukemia was the worst sub-type of AML and most patients die within period of induction of remission because of disseminated intravascular coagulopathy (DIC) and intracranial hemorrhage. Although ATRA has been approved for induction of remission for APL since 1987, this novel drug was only available in clinical use in our country just after 2003.

For the last two decades it has been confirmed that the combination of ATRA and chemotherapy constitute the optimal approach for APL [10].

Most studies were conducted to evaluate the response to ATRA using a dose of 45 mg/m^2 in two divide doses orally with or without chemotherapy[3].

Although ATRA significantly shortens the duration of coagulopathy in comparison with the use of conventional chemotherapy, it does not decrease the number of fatal hemorrhagic death in both arms.[7]

The effect of low dose ATRA (25 mg/m^2) has been studied in a multicentre study conducted by Castiegne et al [12] and revealed similar results in terms of CR rates and pharmacokinetic parameters to ATRA at high doses and estimate that the incidence of hyperleukocytosis and ATRA syndrome was also the same but without statistical significance (27%) since it had reported with standard dose to reach 26% in PITHEMA group (Ortega et al.) (p= .08). This study shed the light on the potentially low side effects of ATRA such as headache and cheilitis, however the long term therapeutic effect of low dose regimen was not evaluated [12].

Because of unavailability of ATRA, and in a hope for less side effects to be experienced by the patients, a low dose regimen had used in this study.

Prophylactic corticosteroids' were used in a try to decrease the incidence of ATRA syndrome depending on previous clinical trials [13].

CR rate in this study was 73% in comparison with 89% in PITHEMA group (Ortega et al.) & 92% in European APL group (Fenaux et al.) (p =.05) & this may be well understood depending on different chemotherapy regimens had been used in combination with ATRA therapy in addition to higher number of cases enrolled in those multi center trials [4,10].

There was a high incidence of induction mortality in this study (27%) comparing with other studies like Ortega et al. in PITHEMA group (11%) or Fenaux

et al. in European APL group (8%) & both carries statistical significance ($p<.05$) [4,10].

This may be probably due to delayed presentation or diagnosis with our patient as those patients who initially presented with major complications were not excluded from the study like those with intracranial hemorrhage, CNS involvement or those with low performance status in addition to the Inadequacy of effective supportive measures (platelets, plasma or cryopreciptate transfusion) and antibiotics.

DFS &OS survival were similar in the current study (86% & 66% respectively) comparing with PITHEMA group (Ortega et al.) (79%&82%) or European APL group (Fenaux et al.) (84% & 82%) showed no statistical significance ($p=.06$) [4,10].

In conclusion ATRA therapy in a dose of $25mg/m^2$ when combined with anthracycline-based chemotherapy achieves CR in the majority of newly diagnosed adults Iraqi patients with AML-M_3 .

The use of low dose ATRA still associated with significant adverse toxic effects and need close follow up.

The followings can be recommended

1. It is wise to use low dose ATRA as management strategy with chemotherapy for the treatment of AML –M_3 when it is unable to start full dose probably because of its availability but further studies are needed to evaluate the long term effect of such therapy.
2. Intensification of the supportive measures during therapy especially in the pre-induction period like blood components and antibiotics to decrease mortality.

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