ATRA (ALLTransretinoic acid) drug in treatment of APL (Acute promylocytic leukemia)

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Background: Acute propmylocytic leukemia APL is a subgroup of acute myeloid leukemia designed as M3 by French American British classification (FAB). The disease characterized by coagulopathy ,association of specific cytogenetic feature of (15-17)translocation .APL constitute less than 10% of all pediatric AML cases. ATRA with its differential action appears to be the inducer of complete remission in APL at diagnosis and relapse .This drug may be associated with side effects like ATRA syndrome .

Objective: To compare the out come of therapy with ATRA vs. Chemotherapy in APL.

Patients &methods: Twenty two 23.9% children with acute promylocytic leukemia were reported for the period 2001-2006 in the central teaching hospital Baghdad , the records were revised regarding using ATRA versus chemotherapy in the induction of APL.

Results: M:F 5:6,The peak age was 10-11 year with mean of 7.5 y , 80.2% were anemic at presentation &thrombocytopenic & for the WBC was 6 x10/AML in our study form 23.9% of all AML. Regarding survival rate for children treated with ATRA & chemotherapy is 87.5%acheved remission. All children had achieved remission while early death occur in one child (12.5%)In comparison to chemotherapy alone 13 death (92.8%) For survival rate after complete remission treated with ATRA or chemotherapy are 37.5%&7.14% subsequently.

Conclusion: Although ATRA provide an important benefit to patient with APL there are significant side effect that may be associated with its use, like ATRA syndrome in 25%.

Key words, APL ,ATRA, children.

Introduction:

Acute propmylocytic leukemia APL is subgroup of acute myeloid leukemia designed as M3 by French American British classification (FAB). The disease characterize by coagulopathy, association of specific cytogenetic feature of (15-17)translocation which involve fusion of APL gene on chromosome 15to the retinoic acid receptor alpha(RARH)on chromosome 17.APL constitute less than 10% of all pediatric AML cases.

ATRA with its differential action appears to be the inducer of complete remission in APL at diagnosis and relapse. This drug may be associated with side effects like ATRA syndrome [1-3].The aim of the study is to find out the percentage of APL among AML children &to determine the result of treatment combination of ATRA& chemotherapy versus chemotherapy alone.

Patients & methods:

Hospital based patients records study carried on ninety four children ,<15 years of age diagnosed as AML between January 2001&August 2006 ,twenty two of them were APL, fourteen were treated with chemotherapy and only eight of them were treated with ATRA on specific protocol applied for treatment of APL **Fig 1.**

The information regarding the age, sex, type of the AML ,complete blood picture , the bone marrow results were taken from the medical records of the patients , there is no facility for chromosomal or cytogenetic study , even the coagulation profile was not of the routine investigation because of the poor resources in our center , the treatment and its complications as well and outcome of the therapy were obtained from the records of patients from the oncology unit of the central teaching hospital for children in Baghdad.

The treatment plan (figure 1)of those eight patients consist of induction treatment with ATRA (25 mg /m/day) orally into two divided doses for thirty days associated with donorubcine (25mg/m/day) for two consecutive days for high risk children, we consider as high risk all patients with WBC >10 $x10^9$/L at diagnosis and those with an increasing leukocytes on follow upWBC on day five>10 $x10^9$/L and day ten WBC>15$x10^9$/L at day fifteen after therapy with ATRA induction when second bone marrow aspiration done .consolidation cycle include three chemotherapy cycles (daunorubcine for two days + standard dose cytarabine; daunorubcine) oral 6

Mercaptopurin and oral methotrexate combined with 14 days ATRA every 3 months was administered for those who obtained complete remission for two years.

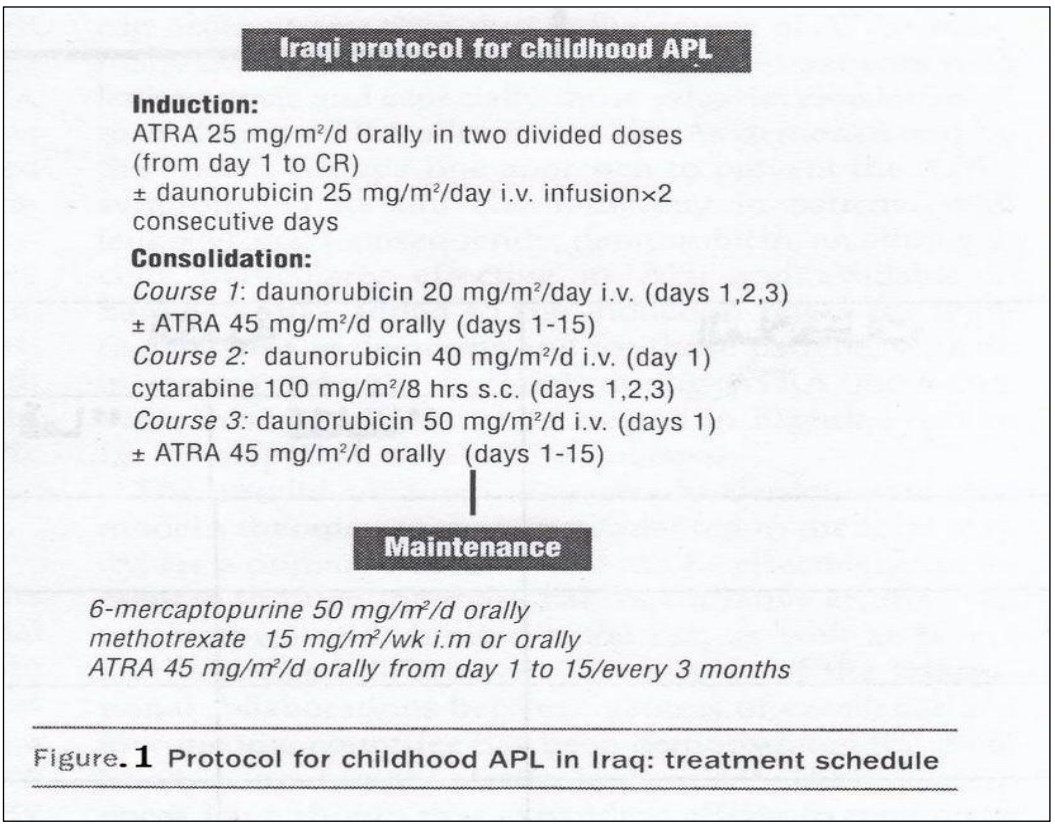

Figure. 1 Protocol for childhood APL in Iraq: treatment schedule

Results

M:F 5:6, the peak age was 10-11 year with median of 7.5 y.

Table(1) show subtypes distribution of AML where M1 constitute 11(11.9%), M2 27(29%) the highest, M3 22(24%) second in rank, M4 15(16.3%), M5(%9), M6 4(4.3%), and M7 6(6.5%).

In table(2) our study in comparison with other world studies show higher % APL than [6*,7,8,9,10,11,] but lower than [6,12].

Table (1) Distribution of AML according to FAB classification

AML type	NO	%	other studies[5]
M1	11	12	20%
M2	27	29	30%
M3	22	24	5-10%
M4	15	16	25-30%
M5	9	9.7	15%
M6	4	4.3	5%
M7	6	6.5	3%
Total	94	100	

Table (2) Proportion of APL in children with AML

STUDY	Reference	%
BFM,1978-1991	6*	3.8
Carter et al	7	6.4
Philip,etal,1972-1987	8	6.6
ARGYLE,ETAL	9	8.7
Gilbert, et al	10	16.3
ALEOP,1989-1993	11**	17.1
Monza,1970-1990	6	30.4
Malta-Corea ,et al,1990-92	12	59.9
Present study		24

*Berlin-Frankfort-Munster childhood leukemia study group
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(Table3)show 17(80.2%)patient with mean HB value of 6.5g/l and normal to leukopenic count with median of $6x10^9$/L and all patients were thropocytopenic.

Table (4 A) show 7 had achieved remission after 30 days ,one died during therapy , three had relapse in the 1st year , only one had early death. Those on chemotherapy alone only one remission and 13(92.8%) had early death , four are still alive , **table (4B)** show longer remission period on ATRA.

Complication of ATRA as seen in **table (5)** was mainly dryness of skin and only 25%had retinoic syndrome.

Table(3) laboratory investigations of children with APL

HB level	**No**	**%**
<6 HB gm/dL	9	40.9
6-8 HBgm/dL	8	39.3
>8 HBgm/dL	5	22.7
WBC	no	%
<4 x10^9/L	9	40.9
4-10 x10^9/L	10	45.4
11-30 x10^9/L	2	9.09
>30 x10^9/L	1	4.5
Platelets	no	%
<20 x10^9/L	14	63.6
>20 x10^9/L	8	39.3

Table(4A) the survival rate of APL children .

Induction phase				
Category	**ATRA& chemotherapy**		**chemotherapy**	
Complete remission	7	87.5%	1	7.14%
Early death	1	12.5%	13	92.8%
Not achieved remission	0	0	0	0

After complete remission(4B)

Category	**ATRA& chemotherapy**		**chemotherapy**	
	No	**%**	**No**	**%**
Relapsed	3	37.5	1	7.14
Period<1 year	2	25		
Death	1	12.5	1	7.14

Table (5) the complication of ATRA therapy

Complications	**No**	**%**
Skin dryness	7	87
Retinoic acid syndrome	2	25
liver enzyme elevation	1	12.5
Headache	2	25
Digestive disturbance	1	12.5

Discussion

Atra doesn't cause lyses but rather the differentiation of the leukemic cells the induction mortality rate mainly due to hemorrhage is significantly reduced and the supportive blood supply is also reduced [(4).]

In our study the percentage of APL was 23.9% of all AML children table [1] ,compared with other studies , our study is lower than Testi etal [4] in which show 35% of cases are APL which is an Iraqi study at the AL Mansour pediatric oncology unit , as well lower than *Fung etal* [2] which show 44.4% of AML cases are APL as well lower than Monza et al [(6)]&Malta etal[12] table (2).

Sex distribution in our study is higher in female than male, not like in the Iraqi study, but different from that in Fung study [2] who show the reverse.

Regarding the age distribution, the peak age was 10-11years with median of 7.5 year while the median age is 11year in Testi etal study[4], but its similar to Fung etal ,the median age is 8.3 year .The lab. data in table(3) show HB was less than 8 gm /dl in 80.2%which is higher than Fung etal[2] in whom 50%had HB<8gm/dl

with mean value of 6.5gm/dl similar to the Iraqi study [4] which may be due to the poor nutritional statues of the children because of the prolonged wars and poverty, for median WBC in this study was $6x10^9$/L similar to [2,5], but for platelets count 63.6%was below 20000cc similar to[2] .

The use of ATRA has provided an alternative mean to induce remission by further differentiation of promylocytes, the use of ATRA for induction in patients may improve the exacerbation of coagulopathy associated with induction chemotherapy [13].

DIC is the most frequently observed in M3 AML , this induction therapy may worsen DIC due to break down of leukemia blasts [5] though we could not study our patient regarding coagulation profile because it is not available in our lab. Because of the poor resources in our hospital, none of our patient develop this complication may be because their count were not high.

Regarding survival rate of children treated with ATRA& chemotherapy or chemotherapy alone as shown in table (4), 7(87.5%) on ATRA regimen had achieved remission which is similar to Steuber, etal (83.7%) [14], three of the seven had relapse (37.5%) two in the 1st year and early death in one child 12.5% in comparison to those on chemotherapy alone, thirteen died early (92.8%) and only one achieved remission of the total 14 children table (4) so the survival was longer on ATRA therapy than on chemotherapy .In our study all children on ATRA achieved remission while Fung etal [2] only 37,5% not achieved remission but there was no early death during induction phase , and was different from [14], where 75% achieved remission &15% had early death, the early death in our study related to the very poor supportive therapy offered by our center because of the poor Iraqi medical care under going in the country .

For survival rate after complete remission table (4B) treated with ATRA or chemotherapy were 37.5%&7.14% respectively which is longer on ATRA therapy again.

In French ATRA group study the event free survival at one year was 83% on ATRA compound to 50% on chemotherapy group(5).

North American inter group ,the over all survival 50%for those assigned to chemotherapy compared to 67% for those assigned to received ATRA(4). It should be recalled that with Atra based regimen 96% of children of children with APL achieve hematological remission and 78% are disease free more than 10 years after diagnosis [5].

Although ATRA provide an important benefit to patient with APL, there is significant side effect that may be associated with it, like pesudotumer cerebri , acute pulmonary edema call ATRA syndrome treated by dexamethasone [5].

In our study the side effect as seen in table(5) mainly dryness of skin &retinoic acid syndrome seen in 25% which is comparable to [15,16] studies where it is mentioned as 3-26% though the study size is small .Recommendation of using ATRA during induction &maintaince therapy & in the post remission period, and the success of this therapy makes marrow transplant in the 1st remission unnecessary for patients with this disease.

Longer period of follow up is recommended with larger study group will give better information about side effect and response of the therapy.

In conclusion M3 in our study is the second most common type of AML after M2 ,combined Atra with chemotherapy improve survival rate ,while Atra syndrome seen in 25% only.

References

1-David G. Tubergen & Archie Bleyer. The leukemia. Nelsson text book of pediatrics 2004, 17th edition ch. 487,page 1697, Sanunders.

2-AWC Fung, SY Ha, CH Hui, Lc Chan, CF chan, YL Lau. Acute promyelocytic leukemia in children. Hong Kong journal of pediatrics1996;1:56-59.

3-Avvisati G. Annolation: acute promyelocytic leukemia .Br J Hematol1992;81:315:20

4-Testi M A,AL Hadad-Jadiry M FF et al: Impact of international collaboration on the prognosis of childhood acute propmylocytic leukemia in Iraq2006,Hematologica:91;509-512.

5-Todd R.Golub Robert J.Arceci.Acute myloid leukemia.principle and practic of oncology by Bizzio ,p564;2003 Lippncott.

6-Cantu-Rajnoldi A, Biondi A, Creutzig U, et al. Diagnosis and incidence of acute promyelocytic leukemia (FAB M3 and M3 Variants) in childhood. Blood 1993;81:2209-10.

7-Carter M, Kalwinsky DK, Dahl GV, et al. Childhood acute promyelocytic leukemia arare variant Of nonlymphoid leukemia with distinctive clinical and biological features. Leukemia , 1989;3:298-302.

8- Phillips M, Richards S, Chessels J. Acute myeloid leukaemia in childhood: the cost and benefits of intensive treatment. Br J Haematol 1991;77:473-7.

9-Argyle JC, Benjamin DR, Lampkin B, et al. Acute nonlymphocytic leukemias of

childhood: inter-observer variability and problems in the use of the FAB classification. Cancer 1989;63:295-301.
10-Gilbert RD, Karabus CD, Mills AE. Acute promyelocytic leukemia a childhood cluster. Cancer 1987;59:933-5.
11-Biondi A, Rovelli A, Cantu-Rajnoldi A, et al. Acute promyelocytic leukemia in children: experience of the Italian Pediatric Hematology and Oncology Group (AIEOP). Leukemia 1994; 8(Suppl 2): S66-70.
12- Malta-Corea A, Pacheco-Espinoza C, Cantu-Rajnoldi A, et al. Childhood acute promyelocytic leukemia in Nicaragua. Ann Oncol 1993;4:892-4.
13-Fenaux P, Dc Botten S. RRTINOIC ACID SYNDROM ,recognition prevention and mangment .Drug Saf 1998;18:273-279.
14-Steuber CP, Civin C ,Krischer d etal : a Comparison of induction and maintance therapy for acute non lymphocytic leukemia in childhood: result of pediatric oncology group study. journal of clinical oncology 1991;9(2):247-258.
15-Bohon S de, Coiteux S ,Chevert C etal : out come of childhood acute promyelocytic leukemia with all tran retinoic acid and chemotherapy . journal of clinical oncology .2004(8):1404-1412.
16-Christopher s, King MD, CPT, MC. John Sherner, MD, CPT, MC. Retinoic acid syndrome: A case report review . the internet journal of oncology .2005.vol. 2 number 2, ISSN:1528-8331.

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