ATRA use in Acute

Promyelocytic Leukemia

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Abbreviation

ALL: Acute Lymphoblastic Leukemia

AML: Acute Myloid Leukemia

APL: Acute Promyelocytic Leukemia

ATRA: AIL-Trans-Retinoic Acid

BM: Bone Marrow

CML: Chronic Myeloid Leukemia

Hb: Hemoglobin

PT: Patient

T : Translocation

WBC: White Blood Cell

Keywords: acute promyelocytic leukemia, ATRA, children

Introduction

Leukemia was first recognized as an entity by Virchow and Bennet independently in 1845 (Virchow 1845; Bennet 1985). The definition of Leukemia by Virchow in 1845 still remains valid today [(1)].

Leukemia:-

Acute Leukemia is a the result of malignant event or events occurring in early hematopoietic precursor, instead of proliferation and differentiation normally, the affect cells give rise to progency that fail to differentiate and instead continue to proliferate in an uncontrolled fashion.

As result immature myeloid cells (in myelogenous Leukemia [AML]) or lymphoid cells (in lymphoblastic leukemia [ALL] often called blasts, rapidly accumulate and progressively replace the bone marrow; diminished production of normal red cell, white cell, platelet ensues [(2)].

Type of childhood leukemia:

In general leukemia are classified into acute (rapidly developing), and chronic (slowly developing) form. in children, about 98% of leukemia are acute.

Acute childhood leukemia are also divided into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), depending whether specific white cell,which are linked to immune defense are involved. [(3)] Approximately 77% of children with leukemia have ALL, about 11% have AML, 2.3% have (chronic myelogenous leukemia [CML]) [(4)].

ACUTE MYELOID LEUKEMIA:

Is a cancer of myeloid cell line of white blood cells, characterized by rapid proliferation of abnormal cells, which accumulate in bone marrow

and interfere with production of normal blood cells. AML is most common acute leukemia affecting adults, and its incidence increase with age [5].

Cellular Classification:

The most comprehensive morphologic-histochemical classification system for AML, was set up by French. American-British (FAB) cooperative group[6,7]. This classification system categorize AML into the following major subtypes:

M_0: acute myeloblastic leukemia without localized differentiation [8].

M_1: acute myeloblastic leukemia without maturation.

M_2: acute myeloblastic leukemia with maturation.

M_3: acute promyelocytic leukemia (APL).

M_4: acute myelomonocytic leukemia (AMML).

M_5: acute monocytic leukemia (AMOL).

M_{2a}: AMOL with out differentiation (monoblast).

M_{5b}: AMOL with differentiation.

M_6: acute erythroleukemia.

M_7: acute megakaryocytic leukemia.

Other types of leukemia include esinophilic leukemia, and acute basophilic leukemia.

Other classification:

World Health Organization Classification (WHO) of AML attempt to become clinically useful to produce more meaningful prognostic information than FAB, criteria.

The WHO subtypes of AML are:

AML with characteristic genetic abnormalities, which include AML with translocation between 8 and 21 [t(8,21)], inversion in chromosome 16 (inv(16)), or translocation between chromosome 15

and 17 [t(15:17)]. Patient with AML in this category generally have a high rate of remission and better prognosis compared with other types of AML. AML with multi lineage dysplasia: this category include patient who have had a prior myelodysplastic syndrome (MDS) or myelproliferative disease (MPD) that transforms into AML. This category of AML occur most often in elderly patient and often hasworse prognosis.

AML and MDS therapy-related: this category include patient who have had prior chemotherapy and/or radiation and subsequently develop AML or MDS. These leukemia may be characterized by specific chromosomal abnormalities and often carry a worse prognosis.

AML not other wise categorized when AML not fall the above categories.

Acute leukemia of ambiguous lineage. This subtype occur when leukemic cells cannot be classified as either myeloid or lymphoid cells, or where both types of cells present. (9)

Signs and symptoms of AML

The signs and symptoms most often seen in AML are:

Anemia causing:

Fatigue are limited capacity of exercises;

Breathlessness on exertion.

Low platelet count causing:

Bruising within the skin.

Bleeding from mucus membrane (e-g gums) and wounds and the gut.

Low (Normal white cells count, high number of abnormal cells and high metabolic rate causing:

Persistant infection.

Fever this is often present even in the absence of clear indication of infection.(10,11)

Less frequent symptoms may relate to tissues infiltration which include enlarged liver, or spleen, enlarged lymph nodes, involvement of central nervous system and chloroma (masses of leukemic cells in skin). (10)

Diagnosis:

The first clue to diagnosis of AML is typically an abnormal result on the complete blood count. While an excess of abnormal white blood cell (W.B.C), (leukocytosis) is common finding, and leukemic blast are some times seen, AML can also present with isolated decrease in platelets, red blood cells, or even with a low white blood cells count (leukopena). [12] while a presumptive diagnosis of AML can be made via examination of peripheral blood smear when are circulating leukemic blasts. A definitive diagnosis usually require adequate bone marrow aspirate and biopsy. Marrow or blood is examined via light microscopy as well as flow cytometry to diagnosis the presence of leukemia and to differentiate AML from other types and to classify the subtypes. A sample of marrow or blood is typically also tested for chromosomal translocat ion, by routine cytogenic or fluorescent in Situ hybridatization. [13]

Acute Promyelocytic Leukemia:

APLwas first recognized as a distinct disease entity in 1957. It's account for 5-10% of cases of AML. The peak incidence of APL is in young adult. APL is consider subtypes of AML and is classified as M_3 variant in FAB classification.[14,15]. This distinct subtypes of AML is associated with abnormal promyelocytes in the blood and bone marrow, associated with consumptive coagulopathy, combining disseminated intravascular coagulopathy, fibrinolysis and proteolysis [16] Further specific chromosomal abnormality[14]represented by a balanced reciprocal translocation between chromosomes 15 and 17, result in the union of portion of the promyelotic leukemia gene with gene for retinoic acidreceptor alpha[17]. This translocation creates a PML/RAB a fusion gene. Itproduce a chimeric protein that arrest the maturation of myeloid cells at promyelocytic stage.

Most APL patient are now treated with ALL-Trans-Retinoic acid (ATRA). ATRA is form of differentiation therapy in which leukemic cells of patient with APL are sensitive to differentiation inducing effect of ATRA.

The basis for this dramatic efficacy of ATRA against APL is the ability of pharmacological dose of ATRA to over come the repression of signaling caused by PML/RARA fusion protein at physiologic ATRA concentration, restoration of signaling leads to differentiation of APL cells and than to post maturation apoptosis.[18] ATRA cannot eliminate the leukemic clone therefore it's used in combination with chemotherapy including an anthracycline drug.[18,20]

ALL-Trans-Retinoic Acid (ATRA):

Tretinoin is the acid form of vitamin A and also known as ATRA. It's drug commonly used to treat acne vulgaris and keratosis pilaris. It's also used to treat APL, more than 95% of it's bind to protein. It's half life is 0.5-2 hours.[20]

Side effects:

Dermatological it causes:

- Dryness of skin
- Redness
- Scaling
- Itching
- Burning
- Extreme sun burn

In leukemia uses:

There is a unique complication of retinoic acid syndrome (RAS) in patient with acute promyelocytic Leukemia. This associated with development of dyspnea, fever, weight gain, peripheral edema and is treated with dexamthasone. The etiology of RAS has been attributed to capillary leak syndrome from cytosine release from differentiating promyelocyte.[21]

Aim

To find out, the percentage of APL from acute myelocytic Leukemia in our center.

To determine the result of treatment combing all-trans-retinoic acid (ATRA) and chemotherapy in childhood acute promyelocytic Leukemia (APL).

Patients and Methods

Retrospective study, carried between January 2001, and August 2006, Ninety four children (c 15 years of ages) were diagnosed as AML by bone marrow examination (aspirate and sometimes biopsy), twenty two of these children diagnosed as APL, fourteen were treated by chemotherapy and eight of these children treated by ATRA and specific protocol.

The information of this study was obtained from files of patients in hematology and oncology unit in central teaching hospital from children regarding age, sex, resistance, type of AML, complete blood count at diagnosis, response to treatment complication during treatment.

The treatment plan of these eight patient in induction was ATRA (25 $mg/m^2/day$) administrated orally in two equally divided doses associated with daunorubicin (25 $mg/m^2/day$) for two consecutive day only for those with WBCc >10 $\times 10^9/L$ at day one, WBCc > $5\times 10^9/L$ at day fifteen at which bone marrow aspiration done this cycle continued for thirty day. In consolidation cycle which includes cycles of daunorubicin stander dose cytorabine by subcutaneous injection with ATRA orally in two divided doses. Oral 6- mercaptopurine and methotrexate combined with ATRA every 3 month was administrated to all patient who obtained complete remission (CR) (<5% blast cells in bone marrow aspirate), for two years this called maintenance stage. All these shown in protocol which is demonstrated.

Daunorubicine only if:

WBC> 10×10^9/L at day 1
WBC>5×10^9/L at day 5
WBC>10×10^9/L at day 10
WBC> 15×10^9/L at day 15

APL protocol M3
Induction

Name:----------
D.O.B:----------
Age: ----------
Wt.: ----------
S.A.: ---------- m^2
B.group:----------
Initial WBCs: ----------

BMA on the 15th day from the initiation of ATRA and on a weekly basis thereafter, until achieving CR or failure

19/11/05

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	----	30
PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD	PRD
ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	Stop after ATRA 8 days	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA

ATRA: 25mg/m^2/day orally in two divided doses and rounded to the nearest 10mg increment, starting on day 1 and continued up to day 30

Daunorubicin: 25mg/m^2/day I.V. infusion over 60 minutes for two successive days

PRD Tranexamic acid 100mg/kg/day as a continuous I.V. infusion only if platelets count < 50.000/cmm
Prednisolone 0.5mg/kg/day from day 1 to the end of therapy with ATRA
Platelets concentrate transfusions to maintain platelets > 20×10^9/L during the first 10 days

APL protocol
HIGH RISK
First Consolidation Course

Name:----------
D.O.B:----------
Age: ----------
Wt.: ----------
S.A.: ----------
B.group:---------
Initial WBCc: ----------

1.3.2005.

ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATR	ATRA	ATRA	ATRA	ATRA	TRA	ATRA	ATRA
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Daunorubicin: 20mg/m^2/day I.V. infusion over 60 minutes day 1,2,3.

ATRA: 45mg/m^2/day orally in two divided doses and rounded to the nearest 10mg increment, starting on day 1 and continued up to day 15

T.MTX **<2y----8mg** **>=2y < 3y----10mg** **>=3y----12mg**

APL protocol
HIGH RISK GROUP
Second consolidation course

Name:----------
D.O.B:----------
Age: ----------
Wt.: ----------
S.A.: ----------
B.group:---------
Initial WBCc: ----------

30-3-05

cytosar	cytosar	cytosar												
ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATR	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Daunorubicin: 40mg/m^2/day I.V. infusion over 60 minutes day 1 only. ☐
Cytosar : 100mg/m^2/dose three times daily(every 8 hours) day 1,2,3 by subcutaneous injection. ☐
ATRA: 45mg/m^2/day orally in two divided doses and rounded to the nearest 10mg increment, starting on day 1 and continued up to day 30 ☐
I.T. MTX. <2y---8mg >=2y <3y----10mg >= 3y---12mg

[redacted]

مع تمنياتنا لكم بالشفاء العاجل

APL protocol
HIGH RISK
Third Consolidation Course

Name:----------
D.O.B:----------
Age: ----------
Wt.: ----------
S.A.: ----------
B.group:---------
Initial WBCc: ----------

ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATR	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA	ATRA
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Daunorubicin: 50mg/m^2/day I.V. infusion over 60 minutes day 1.

ATRA: 45mg/m^2/day orally in two divided doses and rounded to the nearest 10mg increment, starting on day 1 and continued up to day 15

I.T.MTX <2y----8mg >=2y < 3y----10mg >=3y----12mg

A.P.L. MAINTENANCE
COURSE NO.

Name: .....
Age: .....
B. Wt. : .....
S. Area: .....
Initial WBCc .....

Group ( )

Start only if PMN >1.5x10^9/L
And platelets > 100x10^9/L

ANC ☐ ANC ☐ ANC ☐

WEEKS													ATRA	ATRA
6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	28-12-05	
No Rx				No Rx				No Rx					26-9-06	
50%				50%				50%					15-3-06	
75%				75%				75%						
100%				100%				100%						

ATRA: 45mg/m^2/day orally for 15 days every 3 months 40mg

- MTX. 15mg/m^2 P. O. Single dose weekly at least 1hr after the evening meal . 15 mg

Co-trimoxazole in Two consecutive days/wk ? 0.75 → 240mg , 0.76-1m^2 → 360mg , > 1m^2 → 480mg . twice daily

6MP 6-Mercaptopurine 75mg/m^2 P.O. daily , at least 1hr after the evening meal

50% 38mg/m^2 ☐

100% 75mg/m^2 ☐

continue therapy for 24 months i:e:-- 8 cycles
Doses of MTX. and 6MP modified according to WBCc:
WBC between 2.5 and 3.5x10^9/L: dose reduction by 50 %
WBC between < 1.5x 10^9/L: temporary discontinuation of maintenance

Results

Among total 94 cases M1 present in 11 PT (11.9%), M2 in 27 PT (23.9%), M4 in 15 PT (16.3%), M5 in 9 PT (9.7%), M6 in 4 PT (4.3%), M7 in 6 PT (6.5%).

Table (1): The distribution of AML cases according to their morphological subtypes (FAB classification)

AML Type	No. of PT	Percentage %
M1	11	12
M2	27	29
M3	22	24
M4	15	16
M5	9	9.7
M6	4	4.3
M7	6	6.5
Total	94	100

The age distribution of APL patients

The higher incident of APL was in age 10 year (18.1%) and age 11 year (18.1%), and the median of age distribution is 7.5 year.

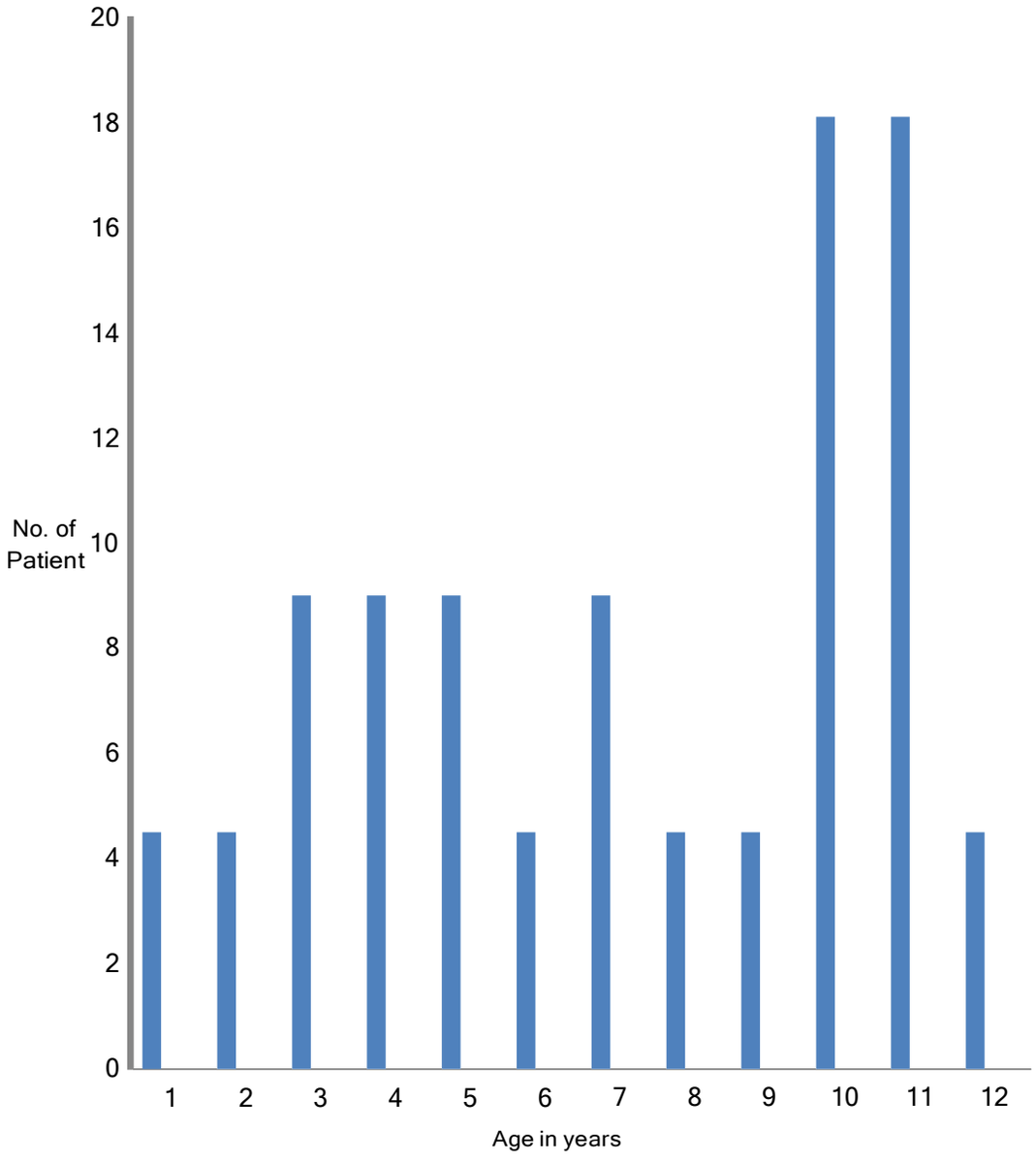
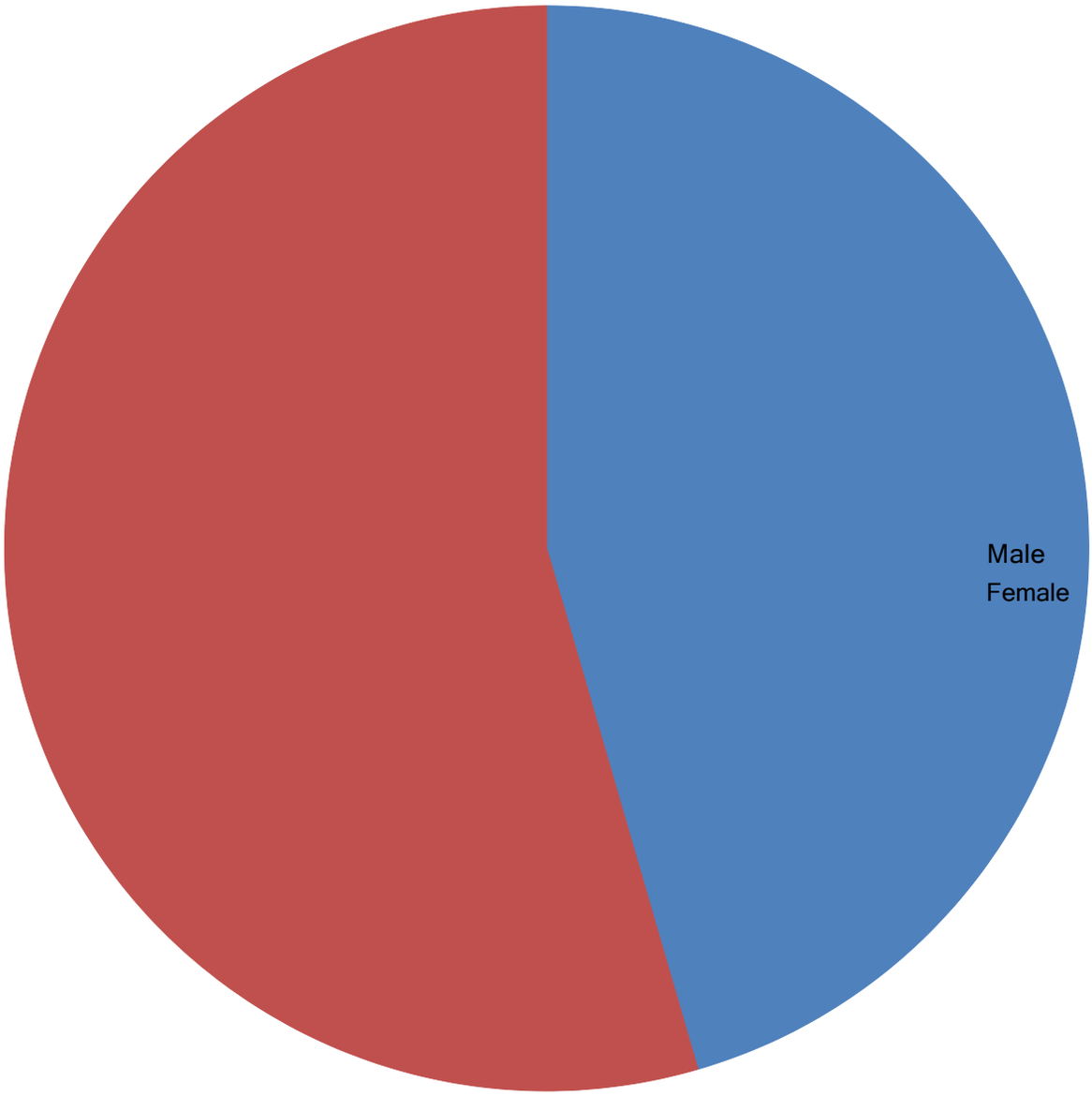


Fig (2): The age distribution of PT with APL



Sex distribution of APL from total 22 PT:

10 PT (45.5%) were male

12 PT (54.5%) were female

Graph (1): Sex Distribution of APL

Distribution of Lab. investigation of patient with APL.

High % of APL patient are anemic Hb<8 g/dl, 17PT(80.2%)with mean Hb value 6.5 g/dl and normal to leukopenic range of W.B.C. count with median count 6×10^9 / L and all PT were thrompocytopenic.

Table (2): Distribution of laboratory investigation of patient with APL.

HB g\dl		
Type of investigation	No. of PT	% of PT
c6	9	40.9
6-8	8	39.3
≥8	5	22.7

W.B.C $\times10^9$/L		
Type of investigation	No. of PT	% of PT
c4	9	40.9
4-10	10	45.4
11-30	2	9.09
≥30	1	4.5

Platelet count $\times10^9$/L		
Type of investigation	No. of PT	% of PT
c20	14	63.6
>20	8	39.3

Distribution of survival rate of APL patient:

From 22 PT. with APL, 8 PT were treated with ATRA and chemotherapy, 7 PT. (87.5%) achieved complete remission after 30 days of treatment, one died during treatment while 14 PT. were treated with chemotherapy, 13 patients (92.8%) of them died during treatment, one PT. (7.14%) achieved remission, after complete remission which achieved by ATRA, 3 patients (37.5%) of 8 patients had relapse 2 of them within 1 year of treatment, and 1 after 1 year, all of them were reinduced one died during reinduction.

Table (3): Distribution of survival rate of APL patients

Induction Cycle				
Category	ATRA and Chemotherapy		Chemotherapy	
	Number	%	Number	%
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				
Category	ATRA and Chemotherapy		Chemotherapy	
	Number	%	Number	%
Relapsed	3	37.5	1	7.14
Period c 1 year	2	25		
Death	1	12.5	1	7.14

Distribution of complication with ATRA

The most common complication of ATRA encountered in patients was dryness of skin and mucosa, found in 7 PT. (87%) Retnoic Acid Syndrome(RAS) occurred in two PT. (25%), elevated liver enzyme in 1 PT (12.5%).

Table (4): Distribution of complication with ATRA

Complication	No. of patients	%
Dryness of skin	7	87
Retinoic acid syndrome	2	25
Elevate liver enzyme	1	12.5
Headache	2	25
Digestive disturbance	1	12.5

Discussion :

The percentage of AML subtypes, 50-60% of children with AML can be classified as having M_1, M_2, M_3, M_6 or M_7, subtypes, these similar to (smith F.O., lampkin B.C., et al).[22] Regarding M_3 alone in our study we found that it's forms (23.9%) of all AML and these percentage lower than what found in(Testi M.A.,AL-Hadad S.A.,et al)(23), in which it forms 35% of all AML.

Regarding a gender predominance, in our study APL was more common in female (54.5%) whereas the male form (45.5%), these disagree with (Fung A.W.C,et al). (24)

Regarding the age distribution majority of patient where between 10 and 11 years and there median age was (7.5 years) these disagree with Testi M.A.,et al (23)in which there median age was (11 years), but our result close to that in Fung A.W.C,et al (24) in which there median age was (8 years).

Regarding laboratory data, in our study (80.2%) were with hemoglobin values less 8 g/dl those less than mentioned in Fung A.W.C,et al.(24) in which (50%) of patient were with hemoglobin values less than 8 g/dl. Regarding W.B.C. count in our study the median of the count was $6*10^9$/l the is same as in Testi M.A.,et al(23). Regarding platelet count ,platelet count less than 20*109/l was found in 63.6%,and this is similar to Fung A.W.C,et al.(24)

Regarding survival rate to those patient treated with ATRA and chemotherapy, in our study 87.5% of patient a achieved remission this percentage similar to Steuber C.P.,et al (25) in which (83.7%) where achieved remission. from those (87.5%) relapse occurred in (37.5%), (25%) within first year of treatment those lower than that in Fung A.W.C,et

al.(24) in which (50%) were relapsed in 1st year of treatment. In our study no patient did not achieved remission and early death occurred in (12.5%) these compared to Fung A.W.C,et al. (24) in which (37.5%) of patient not achieved remission and there was no early death.

Survival rate to those patient who where treated with chemotherapy, in our study only (7.14%) achieved remission and early death occurred in (92.86%) these against Steuber C.P.et al. (25) in which (75%) achieved remission and early death occurred in 15%.

About complication of ATRA the most common complication in the present study is dryness of skin and mucosa (87%) this similar to De-Medeiros B.C.et al (15), in which dryness of skin and mucosa account for 82%. RAS occurred in 25% of patient this is higher than in Botton S.De.,et al(26) in which RAS occurred in (13%) of patient and in De-Medeiros B.C.et al(15) in which RAS occurred in (11%). Elevates liver enzymes occurred in 12.5% of patient while inDe-Mederios B.C.et ab. (15) 19.35% had elevated liver enzymes.

Conclusion:

M_2 subtype of AML is most common subtype.

M_3 second most common subtype of AML with peak age of frequency 10-11 years with female predominance.

Combined ATRA with chemotherapy for treatment of APL improves survival rate of children.

The most common complication of ATRA encounter during treatment was dryness of skin and mucosa.

Recommendation:

Need for further studies in more than one center of oncology and hematology in Iraq to compare the result.

Need for molecular investigation to gain further insight into basic.

Need for regular provision of ATRA.

Need for education program to population about the APL, the management and follow. Up with long time.

Name of the patient:

type of acute myelocytic leukemia

M_1 , M_2 , M_3 , M_4 , M_5 , M_6 , M_7

If M_3

Age

Residence

Complete blood count at diagnosis

Hb W.B.C count platelet count

Type of chemotherapy used in treatment of M_3

Chemotherapy and ATRA or chemotherapy alone

If chemotherapy alone used

- Respone to treatment
  Remission , not achieved remission
  Death during treatment
- Complication during treatment
  Bleeding infection DIC
- After remission relapsed?
  yes or No
- After which period <1year ≥1 from treatment
  Dead reinduced
  If chemotherapy and ATRA used
- Response to treatment
  remission , not achieved , death
- Complication during treatment
  Druness of skin , RAS , elevated liver enzyme
  headache , digestive distrubance
- After achievening remission did they relapsed?
  Yes , no
  After which period ≤1 year , ≥1 year
  dead , reinduced

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