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Original article

ATRA use in Acute Promyelocytic Leukemia

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Abstract:

- ***Background*:** Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) characterized by a specific genetic translocation and favorable response to all-trans-retinoic acid (ATRA). This study aimed to determine the frequency of APL among childhood AML cases and evaluate treatment outcomes using ATRA combined with chemotherapy.
- ***Methods:*** A retrospective study was conducted at the Central Teaching Hospital for Children (2001–2006). Ninety-four children (≤15 years) diagnosed with AML were included. Among them, 22 were identified with APL (FAB M3 subtype). Eight patients received ATRA plus chemotherapy, while 14 received chemotherapy alone. Data on clinical features, lab findings, treatment response, complications, and survival were collected from medical records.
- ***Result:*** APL represented 23.4% of AML cases. Median age was 7.5 years, with 54.5% female. Most patients were anemic (Hb < 8 g/dL in 80.2%) and thrombocytopenic (platelets < 20×10^9/L in 63.6%). Among those treated with ATRA and chemotherapy, 87.5% achieved remission and 12.5% died during induction. In contrast, only 7.1% of patients treated with chemotherapy alone achieved remission, with 92.8% mortality during induction. Relapse occurred in 37.5% of the ATRA group. Common ATRA-related complications included mucocutaneous dryness (87%) and retinoic acid syndrome (25%).
- ***Conclusions:*** APL is a common AML subtype in children. Combined ATRA and chemotherapy significantly improves survival compared to chemotherapy alone. Expanding access to ATRA and molecular diagnostics is essential to improve outcomes in pediatric APL.

- **Keywords:** acute promyelocytic leukemia, ATRA, children

INTRODUCTION

Leukemia was first identified as a distinct disease by Virchow and Bennet independently in 1845 (Virchow 1845; Bennet 1985). The definition provided by Virchow continues to be applicable today (1). Acute leukemia arises from malignant transformation events in early hematopoietic precursors. Instead of undergoing normal proliferation and differentiation, these affected cells produce progeny that fail to mature and instead proliferate uncontrollably. This leads to the accumulation of immature cells—myeloblasts in acute myelogenous leukemia (AML) or lymphoblasts in acute lymphoblastic leukemia (ALL)—which progressively replace normal bone marrow elements, resulting in anemia, neutropenia, and thrombocytopenia (2).

Childhood leukemias are broadly classified into acute (rapid onset) and chronic (slow onset) forms, with approximately 98% of cases being acute. Among these, ALL accounts for about 77%, AML for 11%, and chronic myelogenous leukemia (CML) for 2.3% (3,4).

AML is a malignancy of the myeloid lineage characterized by the rapid proliferation of abnormal myeloid cells, primarily affecting adults with increasing incidence with age (5). The French-American-British (FAB) cooperative group established a morphological and histochemical classification of AML, categorizing it into subtypes M0–M7 (6–8).

Another system, the WHO classification, incorporates cytogenetic and molecular abnormalities to provide better prognostic value (9).

Acute promyelocytic leukemia (APL), classified as M3 in the FAB system, is a distinct AML subtype characterized by abnormal promyelocytes and a high risk of coagulopathy, including disseminated intravascular coagulation (DIC) (14–16). It is associated with a specific translocation t(15;17), resulting in a fusion gene **PML-RARA** that arrests myeloid differentiation (17). APL treatment has been revolutionized by all-trans-retinoic acid (ATRA), a differentiation therapy that restores maturation in leukemic cells. However, ATRA alone is insufficient to eradicate the leukemic clone and is therefore used in combination with anthracycline-based chemotherapy (18,20).

While ATRA has significantly improved outcomes in APL, it is associated with complications such as retinoic acid syndrome (RAS), characterized by dyspnea, fever, edema, and weight gain, attributed to cytokine release from differentiating promyelocytes (21).

This study aims to determine the proportion of APL cases among childhood AML patients at our center and to evaluate the treatment outcomes of ATRA combined with chemotherapy in children with APL.

PATIENT and METHOD

This retrospective study was conducted between January 2001 and August 2006 at the Hematology and Oncology Unit of the Central Teaching Hospital for Children. A total of 94 children aged ≤15 years were diagnosed with acute myeloid leukemia (AML) based on bone marrow examination, including aspirate and, in some cases, biopsy. Among these, 22 patients were identified with acute promyelocytic leukemia (APL) based on morphological criteria (FAB M3 classification).

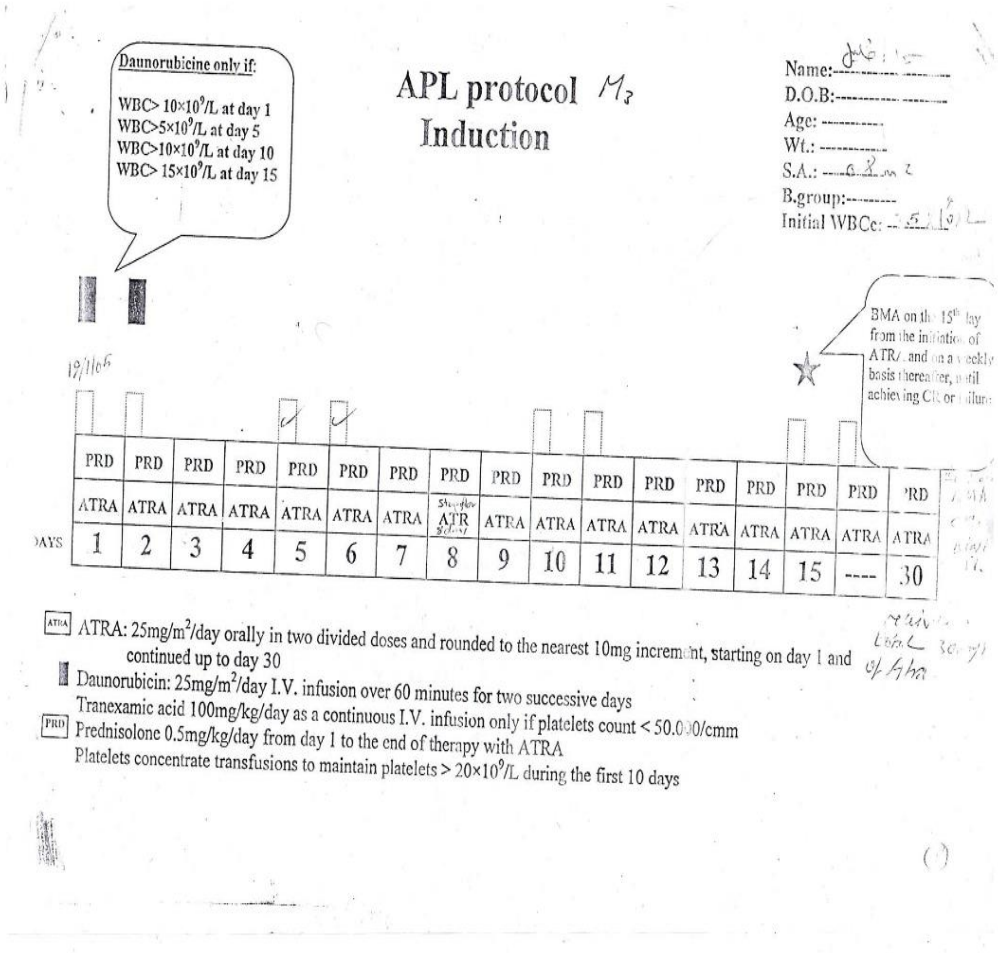
Of the 22 APL patients, 14 received conventional chemotherapy alone, while 8 were treated with a protocol combining all-trans-retinoic acid (ATRA) and chemotherapy. Clinical data were extracted from patient records, including age, sex, residence, AML subtype, complete blood count (CBC) at diagnosis, treatment response, and treatment-related complications.

The treatment protocol for the ATRA group included induction therapy with ATRA at a dose of 25 mg/m²/day administered orally in two divided doses, in combination with daunorubicin at 25 mg/m²/day for two consecutive days. Daunorubicin was

administered only to patients with a white blood cell count (WBC) >10×10^9/L on day one or >5×10^9/L on day fifteen. Bone marrow aspiration was performed on day fifteen, and the induction cycle lasted 30 days.

Consolidation therapy consisted of standard-dose daunorubicin and subcutaneous cytarabine, along with oral ATRA. Patients who achieved complete remission (defined as <5% blasts in bone marrow aspirate) received maintenance therapy for two years. This included oral 6-mercaptopurine, methotrexate, and ATRA every three months.

The full treatment protocol is illustrated and described in the accompanying figures and tables.


Daunorubicine only if:
WBC> 10×10⁹/L at day 1
WBC>5×10⁹/L at day 5
WBC>10×10⁹/L at day 10
WBC> 15×10⁹/L at day 15
APL protocol M3
Induction
Name:
D.O.B:
Age:
Wt.:
S.A.:
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
PRD
ATRA
DAYS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 ---- 30
ATRA: 25mg/m²/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/m²/day I.V. infusion over 60 minutes for two successive days
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 > 20×10⁹/L during the first 10 days

APL protocol
HIGH RISK
Third Consolidation Course

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

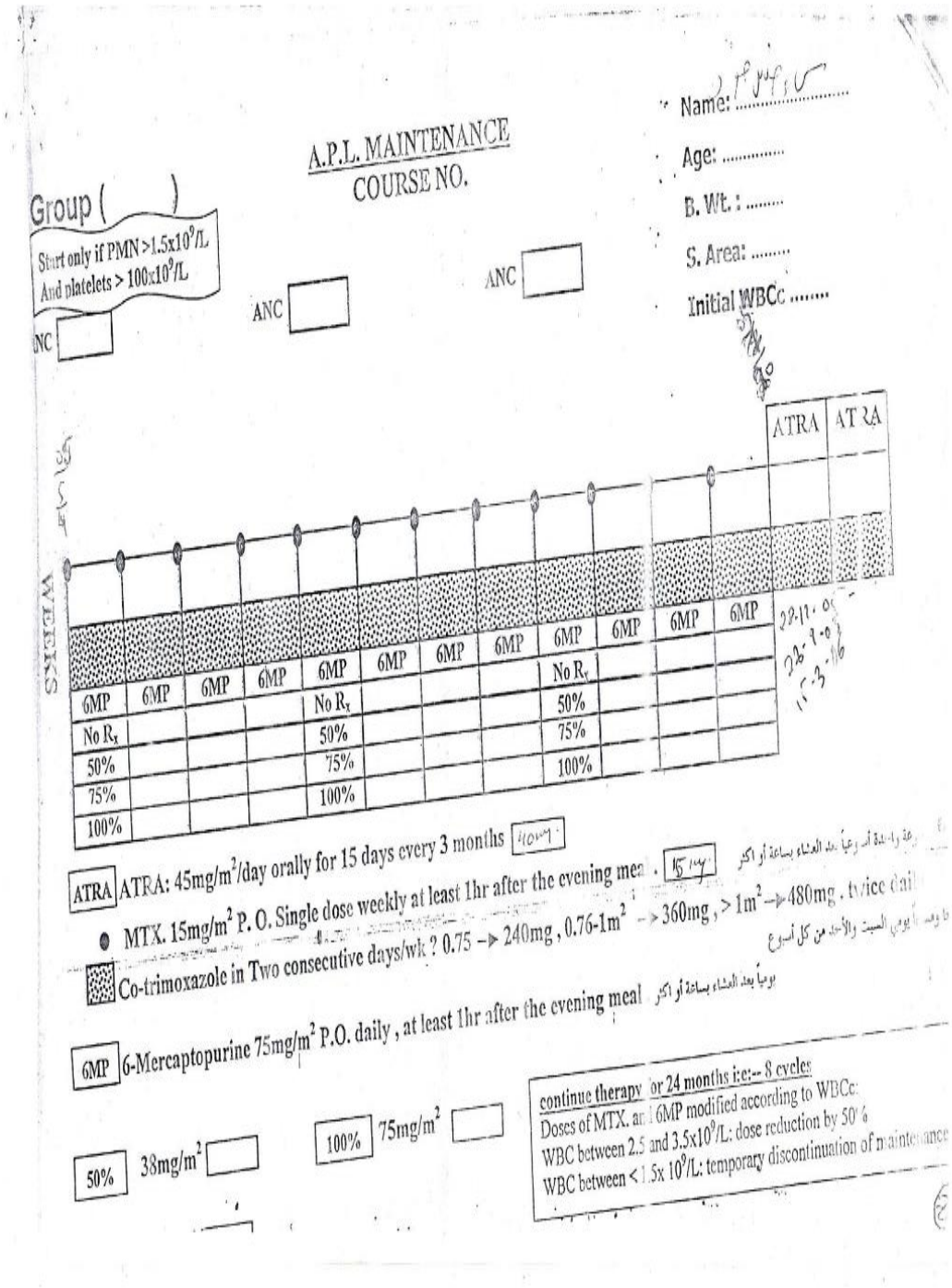
3/4/09

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 >1.5x10⁹/L
And platelets > 100x10⁹/L

ANC ☐ ANC ☐ ANC ☐

WEEKS

ATRA	ATRA												
6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP	6MP			
No Rx				No Rx				No Rx					
50%				50%				50%					
75%				75%				75%					
100%				100%				100%					

ATRA: 45mg/m²/day orally for 15 days every 3 months

MTX. 15mg/m² P. O. Single dose weekly at least 1hr after the evening meal

Co-trimoxazole in Two consecutive days/wk ? 0.75 → 240mg , 0.76-1m² → 360mg , > 1m² → 480mg . twice daily

6MP 6-Mercaptopurine 75mg/m² P.O. daily , at least 1hr after the evening meal

50% 38mg/m² ☐ 100% 75mg/m² ☐

continue therapy for 24 months i.e:-- 8 cycles
Doses of MTX. and 6MP modified according to WBCc:
WBC between 2.5 and 3.5x10⁹/L: dose reduction by 50 %
WBC between < 1.5x 10⁹/L: temporary discontinuation of maintenance

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 (6)

APL protocol
HIGH RISK
First 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	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

RESULTS

Among the 94 children diagnosed with acute myeloid leukemia (AML), the most common morphological subtype was M2 (29%), followed by M3 or acute promyelocytic leukemia (APL) at 24%, M4 at 16%, M1 at 12%, M5 at 9.7%, M7 at 6.5%, and M6 at 4.3% (Table 1).

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

Out of the 22 patients identified with APL, the highest incidence was observed in children aged 10 and 11 years, each accounting for 18.1% of the cases. The median age of presentation was 7.5 years (Figure 1).

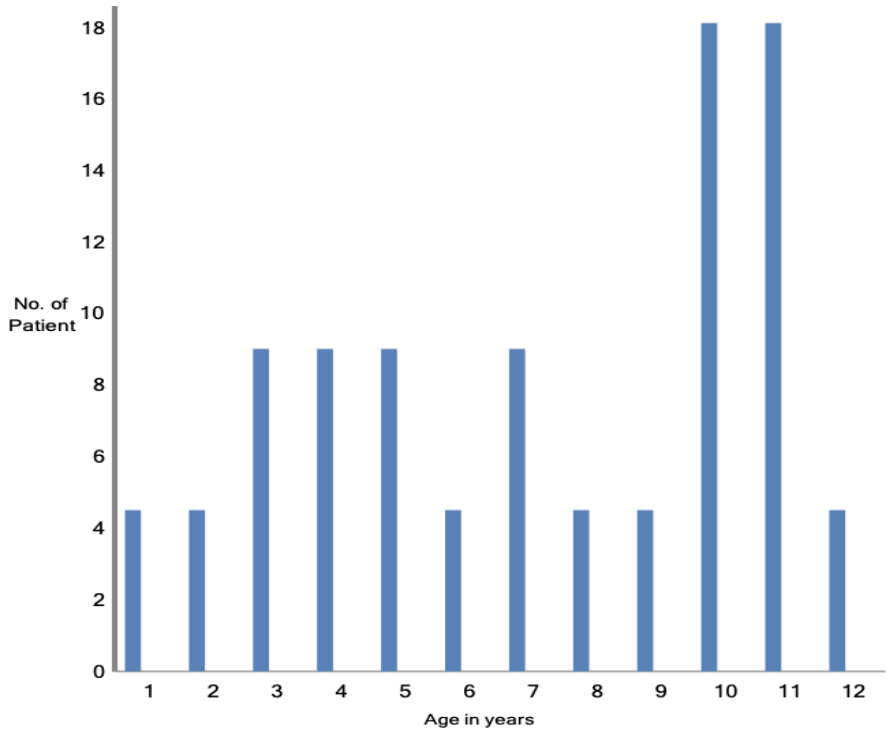


Figure 1. The age distribution of PT with APL

A female predominance was noted, with 54.5% (n=12) of patients being female and 45.5% (n=10) male (Figure 2).

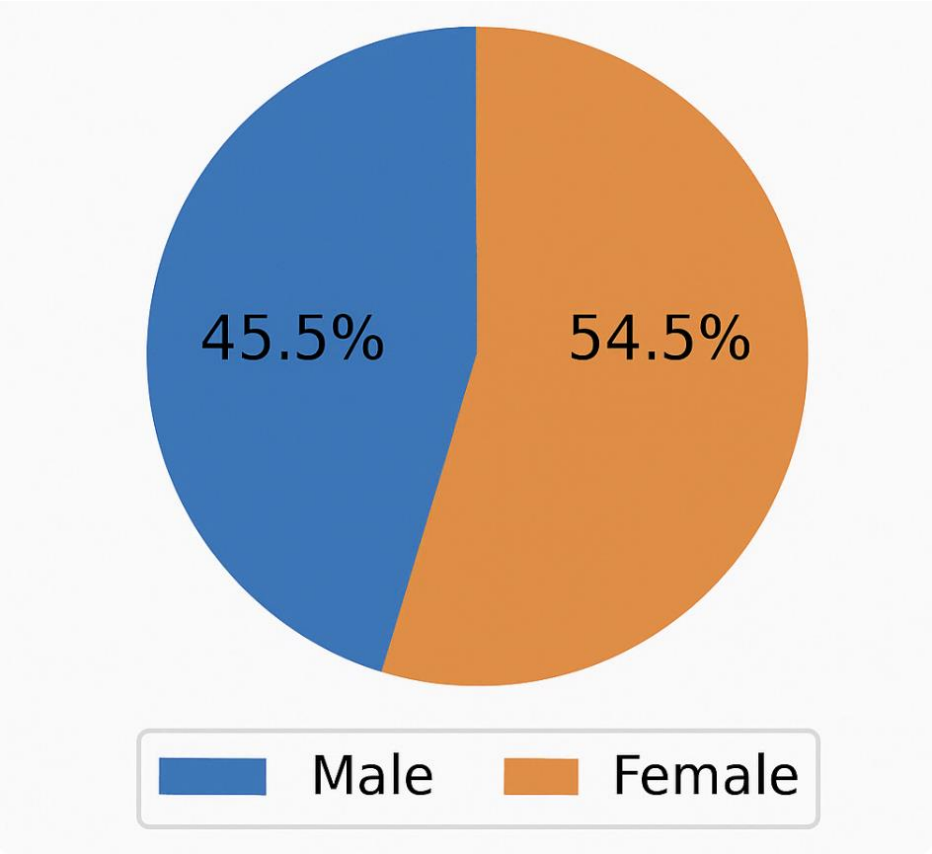


Figure 2. Sex Distribution of APL

Laboratory investigations revealed that 80.2% of APL patients were anemic with hemoglobin levels below 8 g/dL (mean Hb 6.5 g/dL). The white blood cell (WBC) count at diagnosis showed a normal to leukopenic trend, with a median of 6 × 10^9/L. Platelet counts were also markedly reduced, with 63.6% of patients having platelet levels below 20 × 10^9/L (Table 2).

Table (2): Distribution of Laboratory Investigation of Patients with APL

HB g/dL

Type of investigation	No. of PT	% of PT
<6	9	40.9
6–8	8	39.3
≥8	5	22.7

W.B.C ×10⁹/L

Type of investigation	No. of PT	% of PT
<4	9	40.9
4–10	10	45.4
11–30	2	9.09
≥30	1	4.5

Platelet Count ×10⁹/L

Type of investigation	No. of PT	% of PT
<20	14	63.6
>20	8	39.3

Regarding treatment outcomes, of the 8 patients treated with ATRA combined with chemotherapy, 87.5% (n=7) achieved complete remission (CR) after 30 days of induction, and one patient (12.5%) died during treatment. In contrast, among the 14 patients treated with chemotherapy alone, only one (7.14%) achieved CR, while 92.8% (n=13) died during induction. Among those who achieved CR with ATRA-based therapy, 3 patients (37.5%) experienced relapse: two within the first year and one after one year. One of these relapsed patients died during reinduction (Table 3).

Table (3): Distribution of Survival Rate of APL Patients

Induction Cycle

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

The most frequently observed complication of ATRA therapy was dryness of the skin and mucosa, reported in 87% of patients. Retinoic acid syndrome (RAS) occurred in 25%, while elevated liver enzymes, headache, and digestive disturbances were less common (Table 4).

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

In our cohort, the distribution of AML subtypes revealed that 50–60% of pediatric cases fell into the M1, M2, M3, M6, or M7 categories, which is consistent with previous reports by Smith F.O. and Lampkin B.C. et al. (22). Specifically, APL (M3) accounted for 23.9% of all AML cases, which is lower than the 35% reported by Testi M.A., Al-Hadad S.A., et al. (23).

With respect to gender distribution, our study showed a female predominance in APL cases (54.5% female vs. 45.5% male), which contrasts with the findings of Fung A.W.C. et al. who reported a male predominance (24). Age distribution in our patients showed a peak at 10–11 years, with a median age of 7.5 years. This is younger than the 11-year median age reported by Testi M.A. et al. (23), but close to the 8-year median reported by Fung A.W.C. et al. (24).

Hematologic findings in our APL patients demonstrated that 80.2% had hemoglobin levels below 8 g/dL, which is higher than the 50% reported by Fung A.W.C. et al. (24). The median WBC count was 6×10^9/L, consistent with the findings of Testi M.A. et al. (23). Additionally, 63.6% of our patients had platelet counts below 20×10^9/L, similar to data reported by Fung A.W.C. et al. (24).

Regarding treatment outcomes, 87.5% of patients who received ATRA combined with chemotherapy achieved complete remission. This outcome aligns with Steuber C.P. et al., who reported a remission rate of 83.7% (25). Among these responders, 37.5% experienced relapse, with 25% relapsing within the first year. These figures are lower than those reported by Fung A.W.C. et al., where 50% relapsed within the first year (24). Importantly, no patient in the ATRA group failed to achieve remission initially, and early mortality was limited to 12.5%, whereas Fung A.W.C. et al. (24) reported no early deaths but had a 37.5% non-remission rate.

In contrast, among those treated with chemotherapy alone, only 7.14% achieved remission, and early mortality was exceedingly high at 92.86%. These results starkly contrast with the findings of Steuber C.P. et al., who reported a 75% remission rate and 15% early mortality for similar patients (25).

ATRA-related complications in our study were dominated by dryness of the skin and mucosa, occurring in 87% of patients, closely matching the 82% reported by De-

Medeiros B.C. et al. (15). Retinoic acid syndrome (RAS) was observed in 25% of our patients, a higher rate compared to 13% in Botton S. De. et al. (26) and 11% in De-Medeiros B.C. et al. (15). Elevated liver enzymes were seen in 12.5% of our cohort, slightly lower than the 19.35% reported in the latter study (15).

CONCLUSION

The M2 subtype was the most frequently observed variant of acute myeloid leukemia (AML) in this study, followed by the M3 subtype, or acute promyelocytic leukemia (APL), which predominantly affected children aged 10–11 years and showed a slight female predominance. The use of all-trans-retinoic acid (ATRA) in combination with chemotherapy significantly improved survival outcomes in children with APL compared to chemotherapy alone. The most common adverse effect associated with ATRA treatment was dryness of the skin and mucous membranes.

Recommendation

 Multicenter Studies: Further research involving multiple oncology and hematology centers across Iraq is recommended to validate these findings and improve generalizability.

 Molecular Investigations: Incorporation of molecular diagnostics is essential for a deeper understanding of APL pathogenesis and for guiding targeted therapy.

 Medication Access: A consistent and reliable supply of ATRA should be ensured in all pediatric oncology units to support effective treatment.

 Public Awareness and Education: Community-based educational programs are needed to raise awareness about APL, its treatment, and the importance of long-term follow-up in improving outcomes.

Ethical Clearance:

In accordance with the 2013 WMA Helsinki Declaration, all ethical aspects of this study were approved. Before enrolling the participants, an informed oral consent was obtained from their families as an ethical agreement. Additionally, approval from the hospital administrator was obtained.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest**.**

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