Acute promyelocytic leukaemia in children: a thirteen year experience at the child's central teaching hospital

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ABSTRACT

INTRODUCTION: Acute promyelocytic leukaemia (APL) is a rare form of acute myelogenous leukaemia (AML) particularly in children.

OBJECTIVE: To report the clinical characteristics, early induction deaths and outcome regarding patients with APL in one paediatric oncology centre in Baghdad.

METHODS: A descriptive study was conducted at Paediatric Haematology/Oncology unit at the Child's Central Teaching Hospital (CCTH) in Baghdad/ Al-Karkh Health directorate in January 2019. It is a record base study included any patient who was over the age of 15 years diagnosed morphologically as acute promyelocytic leukaemia. Demographic data of the patients, presenting symptoms, response to treatment, and complications were extracted into a form.

RESULTS: Over thirteen year, (21%) of AML patients was diagnosed as APL. The majority of study patients (76%) were considered high risk group. (8.7%) of patients died before initiation of chemotherapy, (16.7%) died during induction and (5%) died in post relapse phase. The events free survival (EFS) was (59%) and the overall survival (OS) was (71%), both were better in low risk group.

CONCLUSION: The survival was better in low risk patients and those with early starting of treatment. This study highlights the need for aggressive supportive treatment during the induction phase to reduce the early mortality rate.

Key words: Acute promyelocytic leukaemia, acute myelogenous leukaemia, ATRA, Iraq.

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INTRODUCTION

Acute promyelocytic leukaemia (APL) is a rare form of acute myelogenous leukaemia (AML) particularly in children, accounting for only 5–7 % of paediatric AML.[1] It is a distinct subtype of AML because of several factors, including the following:

- Clinical presentation of universal coagulopathy (disseminated intravascular coagulation) and unique morphologic characteristics (French-American-British [FAB] M3 or its variants).
- Unique molecular aetiology as a result of the involvement of the retinoic acid receptor-α (RARA) oncogene.
- Unique sensitivity to the differentiating agent all-trans retinoic acid (ATRA) and to the proapoptotic agent arsenic trioxide (ATO).[2]

These unique features of APL mandate a high index of suspicion at diagnosis so as to initiate proper supportive care measures to avoid coagulopathic complications during the first days of therapy. It is also critical to institute a different induction regimen of therapy to minimize the risk of coagulopathic complications and to provide a much-improved long-term relapse-free survival and overall survival (OS) than with past approaches to APL and compared with outcomes for patients with the other forms of

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AML.[3]

Clinically, APL is characterized by severe coagulopathy that is often present at the time of diagnosis.[4] This is typically manifested with thrombocytopenia, prolonged prothrombin time, partial thromboplastin time, elevated d-dimers, and hypofibrinogenemia.[5] Mortality during induction, particularly with cytotoxic agents used alone, caused by bleeding complications is more common in this subtype than in other FAB or World Health Organization (WHO) classifications.[6] Multi-cooperative group analysis of children with APL reported that early induction coagulopathic deaths occurred in 25 of 683 children (3.7%); 23 deaths resulted from haemorrhage (19 CNS, 4 pulmonary), and 2 resulted from CNS thrombosis.[7] A lumbar puncture at diagnosis should not be performed until evidence of coagulopathy has resolved.[7] The risk factors for bleeding complications include high white blood cell (WBC) count (over 10 $\times 10^9$/l), high peripheral blast count (over 30 $\times 10^9$/l), impaired renal function and increased fibrinolysis as reflected by hypofibrinogenemia (<100 mg/dl). Severe thrombocytopenia is generally considered to be a bleeding risk, though in, one series, the platelet count did not correlate with the incidence of bleeding.[8]

Although descriptive studies about PML has been conducted in other oncology centres in Baghdad, this is the first reported study in our centre in which we are trying to identify the clinical characteristics, induction deaths and outcome regarding patients with APL seen in oncology unit/ Child's Central Teaching Hospital.

METHODS

Settings and study design: A retrospective descriptive study conducted in Paediatric Haematology/Oncology unit at the Child's Central Teaching Hospital (CCTH) in Baghdad/ Al-Karkh Health directorate in January 2019.

Ethical consideration: The research protocol was approved by the Arabic council for Health Specializations in Iraq and agreement was taken from the administration of the Child's Central Teaching Hospital to use the records of the patients. The study has been conduced in accordance to the terms of the code of ethics in research of Ministry of Health in Iraq.

Definition of the cases, inclusion and exclusion criteria:

All patients less than 15 years who diagnosed acute promyelocytic leukaemia and was admitted to the Haematology/ Oncology unit at the Child's Central Teaching Hospital during the period from 1st of January 2004, till 31st December 2016 was selected for the analysis with period of follow-up till 31st December 2018. The patients' Data were extracted from the special filling system used in the haematology/oncology unit.

The number of patients diagnosed with AML during the studied period in our centre was 214 patients, 47 of them were diagnosed as APL. One patient was excluded from this study because the diagnosis has changed later on to AML M4.

The diagnosis of APL in our unit during the studied years was established by clinical finding, complete blood count (CBC) and bone marrow (BM) aspiration. Bone marrow was aspirated under general anaesthesia. Leishman stain was usually used to stain the slide, in some patients using cytochemical staining like SBB and PAS, for initial diagnosis and subtypes. Demonstration of abnormal promyelocyte which was larger and typically have creased, folded, bilobed, or kidney-shaped nuclei with heavy azurophilic granules and bundles of Auer rods (faggots) was considered the diagnostic criteria of AP. Immunophenotyping and cytogenetic study of blasts were not used because they were not available in our unit during the studied years.

Treatment response: The treatment response was regularly assessed by bone marrow aspiration, which was performed from day 15 - day 60.

Complete Remission (CR) was defined as the available of all the followings:

- Peripheral blood counts: Leukaemia blasts should not be present in the peripheral blood.
- Bone marrow aspirate and biopsy: <5% blasts with regeneration of normal haematopoiesis.
- Extramedullary leukaemia: such as CNS or soft tissue involvement, may not be present.

Complete first remission (CR1) was estimated after the completion of induction therapy.

Complete second remission (***CR2***), achieving sec-

ond complete remission after relapse.

Partial Remission (PR): The BM is regenerating normal haemopoietic cells and contains between 5 and 15% leukaemic cells.

Resistant Disease (RD): Failure to achieve a CR after induction therapy.

Relapse: Relapse following complete remission, that is defined as reappearance of blasts in the blood or the finding of more than 5% blasts in the BM, not attributable to another cause (e.g., BM regeneration).[9]

Overall Survival (OS): was defined as the length of time from the diagnosis of APL to death from any cause.

Events Free Survival (EFS): was defined as the length of time from diagnosis to the last follow-up or first event: failure to achieve CR, relapse, secondary malignancy, or death from any cause.[10]

Therapy used for patients enrolled in this study:

Supportive: All patients were kept as inpatients for the first 3-4 weeks of treatment. The supportive care at diagnosis before and during therapy were initiated and included hydration, oral allopurinol, antibiotics, blood, platelets, and fresh frozen plasma (FFP) transfusion were given as indicated. The patients were followed-up during treatment by clinical examination and CBC in each visit to Haematology/Oncology consultation clinic.

For those who completed their treatment, follow-up examination and investigation, were scheduled for routine follow-up monthly for the first 6 months, then every 2 months for another 6 months, then every 3 months.[11]

Protocol: Patients were treated according to modified APL protocol for Iraqi children adapted by Italian group. The treatment plan in **Figure 1** consisted of induction treatment with ATRA (25 mg/m^2/day, administered orally in two equally divided doses) for 30 days associated with daunorubicin (25 mg/m^2/day for two consecutive days) only for high-risk patients. We considered as high risk (HR) all patients with a white cell count >10×10^9/L at diagnosis and those with an increasing leukocyte count, defined as follows: white cell count >5×10^9/L at day 5, >10×10^9/L at day 10, or >15×10^9/L at day 15 after the start of

Iraqi protocol for childhood APL

Induction
ATRA 25 mg/m^2/day in two divided doses (from day 1 to CR)
± daunorubicin 25 mg/m^2/day i.v. infusion x2 consecutive days

Consolidation:
Course 1: daunorubicin 20 mg/m2/day i.v. (days 1,2,3)
± ATRA 45 mg/m^2/day orally (days 1-15)
Course 2: daunorubicin 40 mg/m^2/day i.v. (day 1)
cytarabine 100 mg/m2/8 hrs s.c. (days 1,2,3)
Course 3: daunorubicin 50 mg/m^2/d i.v. (day 1)
± ATRA 45 mg/m^2/day orally (days 1-15)

Maintenece
6-Mercaptopurine 50 mg/m^2/day orally
Methotrexate 15 mg/m^2/wk i.m. or orally
ATRA 45 mg/m^2/day orally (days 1-15)/ every 3 months

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

ATRA induction. Consolidation included three chemotherapy cycles (daunorubicin; daunorubicin + standard dose cytarabine by subcutaneous injection; daunorubicin). Both daunorubicin and/or cytarabine were available in Baghdad. ATRA was associated with each consolidation cycle only for high-risk patients. Standard 6-mercaptopurine and methotrexate maintenance with 14 days ATRA, every 3 months, was administered to all patients who had obtained a morphological complete remission for 2 years, from the end of consolidation.

Intrathecal methotrexate prophylaxis (for a total of three doses) was given during each consolidation course to HR patients.[12]

Relapsed patients were treated with different protocols either on old CCTH AML protocol, relapsed APL protocol or ATO ± ATRA protocol.

Statistical analysis: For statistical analysis, the following methods were used: Statistical analysis was performed with the SPSS statistical program version 25. All P values are descriptive and explorative and were considered significant if ≤ 0.05.[13] OS and EFS rates were analysed using the Kaplan–Meier method.

RESULTS

Patient characteristics: The distribution of study patients by socio-demographic data is shown in

Table 1: Distribution of study patients by age and gender

Variable	No. (n= 46)	Percentage (%)
Age (Years)		
≤ 5	13	28.3
> 5	33	71.7
Gender		
Male	27	58.7
Female	19	41.3

Table 2: Clinical presentation of study patients

Clinical Presentation *	No. (n= 46)	Percentage (%)
Fever	41	89.1
Pallor	43	93.5
Bleeding	36	78.3
Bone Pain	19	41.3
Loss of Weight	6	13.0
Hepatomegaly	13	28.3
Splenomegaly	7	15.2
LAP	6	13.0
Ecchymosis	31	67.4
Duration of Symptoms (Weeks)		
< 6	40	87.0
≥ 6	6	13.0

* Some of patients presented with more than one presentation, so the total no. of presentations is more than the total no. of patients.

Table 3: Distribution of study patients by investigation

Investigation	No. (n= 46)	Percentage (%)
PCV (%)		
< 30	25	93.4
> 30	3	6.6
WBC Count (×10⁹ / L)		
< 10	27	58.7
≥ 10	19	41.3
Platelet Count (×10⁹ / L)		
< 30	32	69.6
≥ 30	14	30.4
Cytospin		
Positive	3	6
Negative	22	47
Not done	21	45
Coagulopathy (PT, PTT)		
Done	6	13
Not assessed *	40	87
Bone Marrow Morphology		
AML-M3	36	78.3
AML-M3v	10	21.7
Risk Group		
High Risk	35	76
Low Risk	11	24

*Either not done or not recorded in files

table 1. Patient's age was ranging from two to 13 years with a mean of 8.13 years. The highest proportion of study patients was older than five years (71.7%). Regarding gender, proportion of males was higher than females (58.7% versus 41.3%) with a male to female ratio of 1.42:1.

Table 2 shows the clinical presentation of the patients enrolled in this study. The most common clinical presentation was pallor (93.5%) followed by fever (89.1%) and bleeding (78.3%).

Investigations: In this study, patients PCV was ranging from 13% - 57% with a mean of 22.91% ± 7.52%. Majority of them showed a PCV less than 30% (93.4%). Regarding initial WBC count, it was ranging from 0.5 – 173 (×10⁹/L) with a mean of 20.27 ± 34.07 (×10⁹/L). The highest proportion of study patients showed a WBC count < 10 (×10⁹/L) (58.7%). Platelet count was ranging from 5 – 220 (×10⁹/L) with a mean of 28.99 ± 33.46 (×10⁹/L).

About bone marrow morphology, the majority of the patients were diagnosed as APL-M3 (78.3%) and 76% of them were considered a high risk group (all patients with a white cell count >10×10⁹/L at diagnosis and those with an increasing leukocyte count during follow up after the start of ATRA induction) as shown in table 3.

Fate of patients since diagnosis: Table 4 shows the fate of the patients since diagnosis. In the pre-induction phase, four patients (8.7%) died before initiation of chemotherapy, all died due to coagulopathy.

Regarding induction phase: 42 patients received induction. During induction phase, seven patients (16.7%) died with a median of 12 days (range from 4 – 28 days); and 35 (83%)

Table 4: Fate of study patients since diagnosis

Phase	No.	(%)
Pre-Induction (n = 46)		
Not Received Treatment (Very Early Death)	4	8.7
Started Treatment	42	91.3
Induction (n = 42)		
Death during Induction	7	16.7
CR	35	83.3
Post-Induction (n = 35)		
Relapse	10	28.6
CCR	25	71.4

Table 5: Characteristics of induction-death patients

No.	Age (Years)	Gender	BM Subtype	Duration since diagnosis (Days)	Cause of Death	Risk Group
1	5	Female	M3	7	Bleeding	High Risk
2	9	Female	M3v	20	Bleeding	Low Risk
3	13	Male	M3	3	Differentiation syndrome	Low Risk
4	7	Female	M3v	15	Bleeding	High Risk
5	5	Male	M3v	90	ICH	High Risk
6	7	Female	M3v	7	ICH	High Risk
7	4	Female	M3	10	ICH	High Risk

Table 6: Characteristics of relapsed patients

No.	Age (Years)	Gender	BM Subtype	Risk Group	Rx Protocol after relapse	Fate
1	7	Male	M3	Low Risk	CCTH AML Protocol	Died
2	10	Male	M3	Low Risk	APL Relapse Protocol	Died
3	12	Male	M3	High Risk	APL Relapse Protocol	Died
4	12	Male	M3v	High Risk	APL Relapse Protocol	Died
5	5	Male	M3	High Risk	ATO Protocol	Died
6	12	Female	M3	High Risk	APL protocol	Alive
7	9	Male	M3	High Risk	ATO Protocol	Alive
8	5	Male	M3	High Risk	ATO +ATRA Protocol	Alive
9	6	Male	M3v	High Risk	APL Protocol	Alive
10	5	Male	M3	High Risk	Relapse Rx of AML In CCTH Protocol	Loss to follow up

patients have complete remission during induction. About post induction phase, 35 patients received consolidation and maintenance treatment; 10 of them (28.6%) relapsed and 25 (71.4%) had continuous complete remission (CCR).

Induction-death patients: In this study, seven patients were died during induction, five of them were considered as a high risk group. The most common cause of death was coagulopathy.

Relapsed patients: Ten patients relapsed during this study, eight (80%) of patients were high risk group. Five patients died, one patient lost his follow up and four patients had second remission CR2, from those who had second remission two received ATO as post relapse treatment.

Event Free Survival (EFS) and Overall Survival (OS): Figure 2 and figure 3 show the EFS was 59% and the OS was 71%. Figure 4 shows the EFS according to risk group. We noticed that low risk was better than high risk but this difference was statistically not significant (100% versus 90%, P=

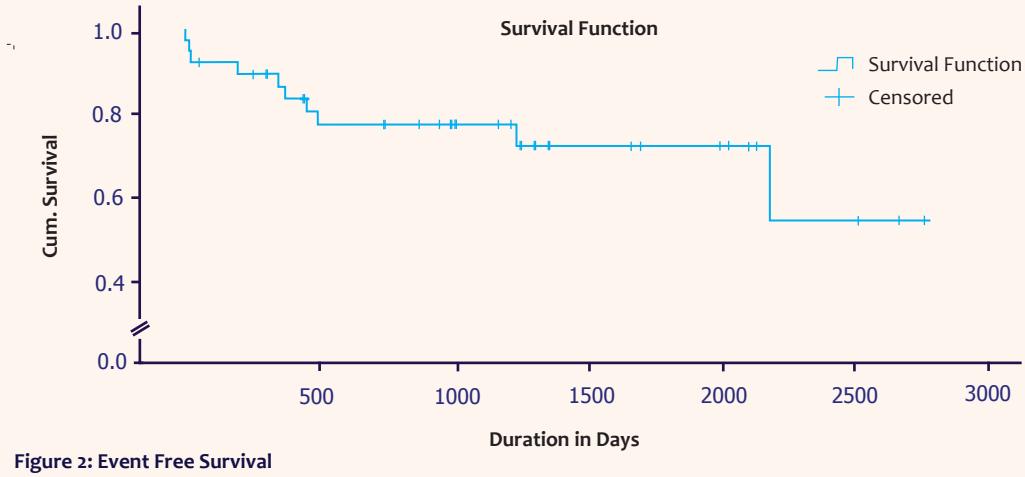

Figure 2: Event Free Survival

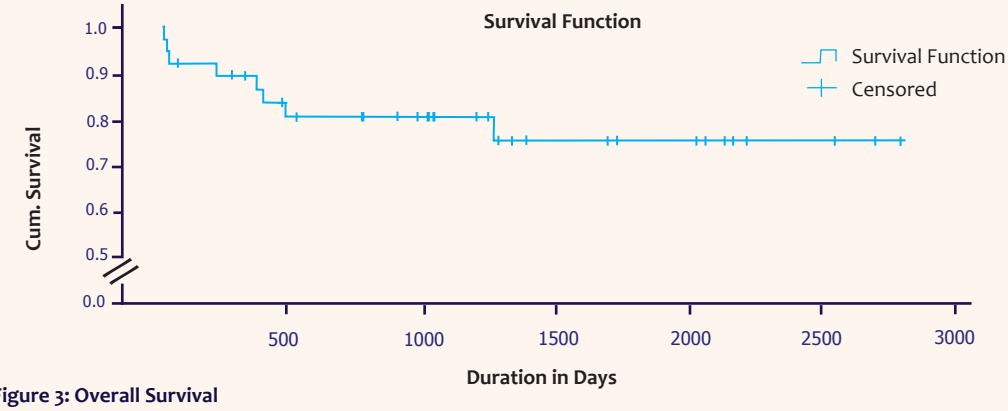

Figure 3: Overall Survival

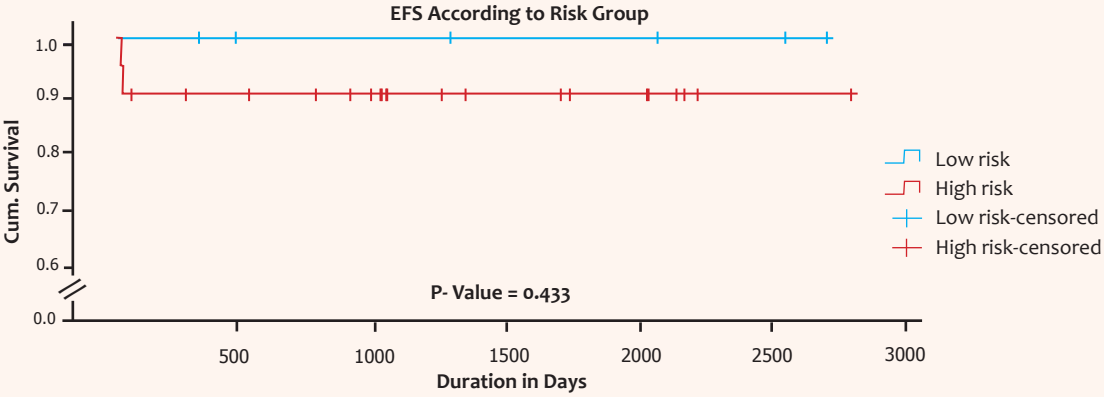

Figure 4: EFS according to risk group

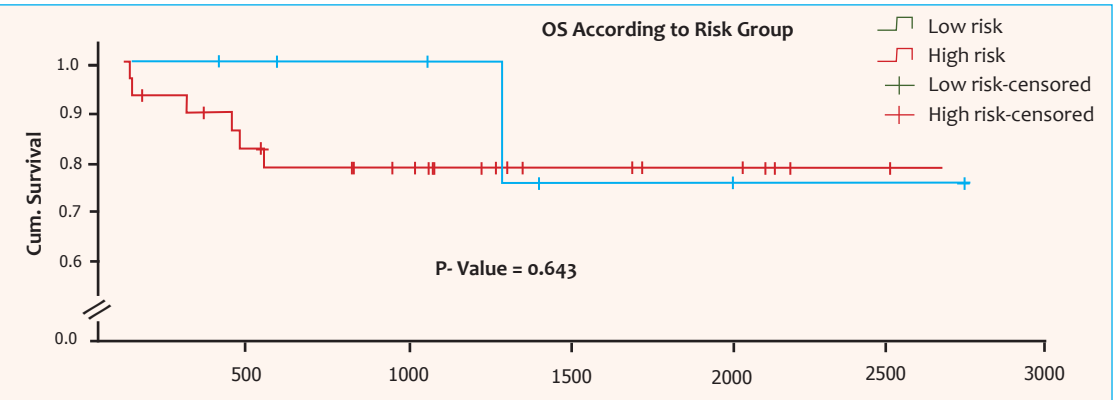

Figure 5: OS according to risk group

0.433).

Figure 5 shows the OS according to risk group. Low risk was better than high risk but this difference was statistically not significant (85.7% versus 79.3%, P= 0.643).

DISCUSSION

Acute promyelocytic leukaemia (APL) is a unique subtype of the acute leukaemia's. In our study, 46 patients were having APL out of 214 patients diagnosed as AML (21 %). This rate is higher than what has been reported from United States, and in Central and Northern Europe, where the percentage of APL patients is 5-7 % of all paediatric AML cases;[14] but it seems to be similar to frequency reported in children of Latino/Hispanic descent which was about 20%.[15] In Iraq, in a study conducted in Al Mansour Hos-

pital for Paediatrics in Baghdad in 2006 has reported that APL diagnosed morphologically was about 30 % of paediatric AML.[12] The presumed higher prevalence of APL may reflect underestimation of AML cases. Ethnic variability may also account for this high incidence of APL in the various countries; environmental factors may play a role. In addition, the diagnostic poor facilities have to be considered as possible bias for the reported higher incidence of childhood APL in the developing countries.[1]

The mean age of patients with APL was 8.13 years, about 28 % of them was less than five years. This agrees with Japanese paediatric leukaemia/ lymphoma study group in which the median age at diagnosis was 9 years, about 25 % were less than 5 years of age at diagnosis.[10] In most countries, the incidence of the disease increases during second decade of life.[16]

The study shows male predominance of 1.42:1 similar to other local and international studies; Al-Hadad study (2:1)[12], W. Jastaniah et al in Saudi Arabia (1.8:1).[17] However, A study from Children Welfare Teaching Hospital (CWTH) in Baghdad by Ali RZ[18] and A French paediatric study published by de Botton et al[19] showed the predominance of female.

In our study, fever was presented in 89.1 % of patients with APL which was similar to that reported by Al-Hadad[12] but it is higher than that reported by Ali RZ[18] and Testi et al.[20] The study also showed that 78.3% of patients with APL were presented with bleeding; it is comparable to that reported by Al-Hadad, Ali RZ, and Testi et al.[12,18,20] Bleeding secondary to disseminated intravascular coagulopathy (DIC) is a unique presentation at diagnosis or after the initiation of cytotoxic chemotherapy in patients with APL.[21]

The majority of patients (93.4%) presented with a PCV of less than 30%, nearly similar to that reported by Ali RZ (95.6%) and Al-Hadad study (100%).[12,18]

In 41.3% of patients the initial WBC count was equal or more than 10×109/l, The proportion of patients was comparable to that reported by others.[19,20,22] Using the commonly adopted cut-off value of $10x10^9$/l, the incidence of hyper leukocytosis is clearly higher in children than in adolescents and in adults, in whom it is usually around 20% to 25%.[16,23] In the Berlin-Frankfurt-Münster paediatric APL series, 30/81 children (30%) presented WBC ≥ $10x10^9$/l.[24] Higher percentages seen in CWTH (60.9%), and in Saudi Arabian study of childhood APL (57%) who had hyper leukocytosis at disease presentation.[17,18] The mean platelet count was $28.99×10^9$/l this is nearly similar to that seen by Ali RZ.[18]

Microgranular M3v was reported in our series in 21.7 % of patients with APL. De Botton[19] has shown that M3v is more in children compared to adults 25 % versus 12%. A prevalence of M3v as high as 32 % has been reported children with APL in some series. Bally also found a prevalence M3v of 24 % in patients 13-18 years.[23] Similarly, M3v were found not to be increased in the AIEOP-GIMEMA and PETHEMA studies when compared to adults.[20,25]

The true incidence of CNS involvement at diagnosis is unknown both in children and adults. In this study, cytospin (cytocentrifuge of cerebrospinal fluid (CSF)) has not been done 21 patients (45%); from the remaining 25 patients, only 3 were positive (12%). This result is compatible to the 13 % reported by Jastaniah et al,[17] in contrary Ali RZ[18] has reported that none in his series showed a positive (CSF) at diagnosis.

In the pre-induction phase, four patients (8.7 %) died within 7 days from diagnosis. Compared to a study conducted in Baghdad in 2006,[18] this study showed a lower mortality rate due to better and aggressive supportive measures especially the availability of fresh platelets in our hospital.

Since the introduction of ATRA, the early death, mainly because of bleeding, is dramatically reduced to about 3-7 % in paediatric APL studies; similar results have been reported in most of adult cooperative group trials (5-10%).[26]

In our settings as a developing country, and as a country with different continuous crises, the patients are usually referred late to our centre which might contribute to the delay in diagnosis and immediate initiation of treatment. Some of our patients were not fit to receive chemotherapy because they were too ill at time of admission and died of CNS bleeding.

Regarding induction phase: 42 patients received induction; 35 (83%) patients have complete remission during induction and seven (16.7%) of them were died during induction,

but there is no induction failure. Recent clinical studies of childhood APL,[19,20,22] have stated that induction therapy with ATRA and anthracyclines with or without cytarabine achieved CR rates of > 90% and incidence of early death of <10% . This higher ratio of induction death than other studies could be due to poor and inadequate supportive care facilities and our trend to use less intensified treatment.

Death during induction phase has seen to be more in those considered as a high risk group. This logical correlation agrees with that reported by Testi et al in which all children died during induction were of high risk group.[20] So, the state-of-the-art treatment guidelines[27] Recommends that anthracyclines should be started together with ATRA (or as soon as possible) in high-risk patients.

In our study, coagulopathy was the commonest cause of death during induction; only one patients died due to differentiation syndrome. Creutzig et al[24] has reported that 3 out 5 (60%) children died during induction phase was due to haemorrhage, one patient died from sepsis in aplasia and another one from differentiation syndrome. In Imaizumi et al study,[28] all death during induction was due to haemorrhage. Testi also reported that intracerebral haemorrhage was the cause of death in 75% and the other 25% occurred due to severe infection.[20] Disseminated intravascular coagulation and APL-Differentiation syndrome are the major life-threatening complications that develop during remission induction therapy in APL.[27]

Ten patients (28.6%) relapsed during this study, eight of them (80%) were of high risk group; five died, four remained in CR2 and one lost to follow up. Our relapsing rate seems similar to that reported by Bally,[23] but less than that reported by Ali,[18] Ortega,[22] Creutsig,[24] and Imaizumi[28] who reported the rate to be 22, 23, 17, and 11 % respectively. Many studies[18,22,23,24,28] agree with ours that relapsing rate is more frequent in patients of high risk group.

In the paediatric series of GIMEMA-AIEOP AIDA 0493 trial, a leukocyte count at diagnosis ≥ 10 x109/l had a negative impact incidence of relapse, among the 61 children treated with PETHEMA trials, relapse was higher for those with presenting WBC ≥ 10x10^9/l, compared to those with lower WBC count (31% vs. 3.5%).[20,22]

In this study, four (40%) of relapsed patients remained in continuous complete remission CR2; while in Ali RZ[18] study only one (14%) of relapsed patients remained in CCR2.

Two of patients who achieved CR2 received ATO ± ATRA and 2 of them received same APL protocol used for induction in CCTH. This rate supports the use of ATO ± ATRA for relapsed patients.

The EFS was (59%) this comparable to CWTH study (61%) and Saudi Arabian study (55%). about the OS was (71%) in present study, higher than CWTH study (63.4%) but near the rate of Saudi Arabian study (74%).[17,18] But EFS and OS rates were lower than what has been published elsewhere, 59% in our study vs. (>70%) in many others and OS (71%) in our study vs. rates were (> 80%) in others. [20,22,29]

According to risk groups, both EFS and OS were better in LR than HR. In the present study, (76%) of patients were high risk compared to the (35–48%) range reported in other studies. Thus the inferior EFS and OS outcomes are likely related to the fact that a relatively higher proportion of patients in the present study were high risk. [20,22,29]

CONCLUSION

Overall high incidence of childhood APL is recorded in CCTH. Induction death was still high and it was seen more in high risk group. Bleeding remains the most common cause of induction death. Remission. The survival rate was less than international studies and they were less in high risk group.

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Abbreviation list: Acute promyelocytic leukaemia (**APL**), Acute myelogenous leukaemia (**AML**), All-trans retinoic acid (**ATRA**), Arsenic trioxide (**ATO**), Bone marrow (**BM**), Central nervous system (**CNS**), Cerebrospinal fluid (**CSF**), Children Welfare Teaching Hospital (**CWTH**), Child's Central Teaching Hospital (**CCTH**), Complete blood count (**CBC**), Complete First Remission (**CR1**), Complete Remission (**CR**), Complete Second Remission (**CR2**), Continuous complete remission (**CCR**), Disseminated intravascular coagulopathy (**DIC**), Events Free Survival (**EFS**), French-American-British (**FAB**), Fresh frozen plasma (**FFP**), Intra Cranial Haemorrhage (**ICH**), Litter (**l**), milligram per decilitre (**mg/dl**), Overall survival (**OS**), Partial Remission (**PR**), Resistant Disease (**RD**), Retinoic acid receptor-α (**RARA**), Statistical Package for Social Science (**SPSS**), White blood cell (**WBC**), World Health Organization (**WHO**).

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