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# Acute promyelocytic leukemia: Epidemiology, clinical presentation, and outcome over a 10-year period of follow-up at Nanakali Hospital of Erbil city "Single-center study"

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**Abstract:**

**BACKGROUND:** Among the subtypes of acute myeloid leukemia, acute promyelocytic leukemia (APL) is a distinctive one. There are no published data regarding APL in Kurdistan, Iraq, so the data on this disease is limited.

**OBJECTIVES:** The aims of this study was to recognize the epidemiology, clinical presentation, and to find out the outcome among APL patients at Nanakali hospital in Erbil city.

**PATIENTS AND METHODS:** This was a retrospective study performed at Nanakali Hospital for blood diseases and cancer, Erbil, Iraq. Patients older than 18 years diagnosed with APL from January 2007 to December 2016 were involved in the study. Chi-square test, Kaplan–Meier survival curves, and the Log-Rank (Mantel–Cox) test were used for data analysis.

**RESULTS:** During the period of the study, APL was diagnosed in 90 patients. The mean age (± standard deviations) was 37.5 ± 15.5 years, and the median was 35.5 years, the male: female ratio was 1.3:1. Around 70% were living in urban areas. Regarding clinical presentations: 71.4% of the patients presented with generalized weakness, 64.44% with bleeding, 48.9% with fever, and 2.2% presented with thrombosis. The mean hemoglobin was 8.31 ± 2.69 g/dL, mean white blood cell count of 22.3 ± 29.4 × $10^9$/L, and mean platelet count was 33.37 ± 27.5 × $10^9$/L. The complete remission rate was 68.2%. Early death rate was 46.4% and the 5-year survival rate was 37.8%.

**CONCLUSION:** The clinical and epidemiological features were compared with previously published studies. High-risk patients predominate in our study population. There was a significant association between the overall survival and risk score.

**Keywords:**

Acute promyelocytic leukemia, Erbil, Iraq

## Introduction

In 1957, acute promyelocytic leukemia (APL) was recognized as a unique subtype of acute myeloid leukemia (AML), representing 5%–15% of total AML cases.[1] The reciprocal translocation between chromosome 15 and 17 in addition to the morphological features are used for the identification of this disease.[2] APL has the highest cure rate among AML subtypes.[3,4]

There are limited reports on the epidemiology of APL.[5] However, in the recent years, there was increased interest in the epidemiology of the specific types of leukemia. Since APL is a rare disease, epidemiologic data on this

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disease can be acquired only from large collaborative multicenter researches.[6]

In the period that preceded the discovery of differentiating agents like all-trans retinoic acid (ATRA) in the mid-1980s and arsenic trioxide (ATO) in 1996, APL was associated with high rates of mortality because of bleeding complications during induction therapy.[7] With the introduction of these agents, the natural history of APL had changed, as they induce differentiation and maturation of leukemic promyelocytes to neutrophils.[8-10]

Bleeding complications, infections, and differentiation syndrome (DS) are important causes of induction failure and mortality,[11,12] on the other hand, unresponsiveness to treatment is rarely encountered during the induction phase.[8,13]

There are no published data regarding APL in Kurdistan, Iraq, so the records on this disease are limited. The aims of this study was to recognize the epidemiology, clinical presentation, and to find out the outcome among APL patients in our center in Erbil city.

## Patients and Methods

This retrospective, descriptive study was carried out at Nanakali Hospital for blood diseases and cancer in Erbil. Nanakali Center is a 100-bed tertiary care hospital that receives pediatric and adult patients with benign and malignant hematological diseases and solid tumors.

### Inclusion and exclusion criteria

All APL patients who were ≥18 years old from January 2007 to December 2016 were reviewed. The diagnosis of APL was based on French–American–British classification system. Cytogenetics and flow cytometry were done whenever possible. Patients with age <18 years old were excluded from the study, 6 patients left the hospital after diagnosis so they were excluded from the final analysis of overall survival.

Risk stratification was done for the patients according to Sanz risk score which classified patients into three groups depending on their initial white blood cell (WBC) and platelet counts.[14]

- High risk: When the presenting WBC count >10 × $10^9$/L irrespective of platelets counts
- Intermediate risk: When the presenting WBC count ≤10 × $10^9$/L and platelets ≤40 × $10^9$/L
- Low risk: Those patients had WBC ≤10 × $10^9$/L, but their platelet count is >40 × $10^9$/L.

Hemoglobin more than 10 g/dL without transfusion, absolute neutrophil count more than 1.5 × $10^9$/L, platelet count more than 100 × $10^9$/L, and a normocellular bone marrow with <5% blasts plus promyelocytes were required to achieve complete remission (CR) after induction therapy.

The basis of the treatment protocol was combination of ATRA and anthracycline (idarubicin, daunorubicin, or adriamycin). Cytarabine was added in the high-risk category. Dose modification was considered in old age patients with comorbidities.

Our study had been approved by the ethical committee of our institution, the Kurdistan Board for Medical Specialties, written informed consent was obtained from alive patients before registration.

### Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version22, IBM, NY, United States of America). Categorical variables were presented as proportions, while numerical variables were summarized by means and standard deviations (SDs). The Chi-square test of association was used to compare proportions. Kaplan–Meier survival curves had been plotted for the three risk categories and the log-rank (Mantel–Cox) test was used to compare the mean survival times and to show whether there is significant difference or not between the survival times. $P \leq 0.05$ was considered statistically significant.

## Results

From January 2007 to December 2016, 683 patients were diagnosed with AML in our center, ninety patients with APL (13.1%) had been involved in the study. Their mean age (±SD) was 37.5 ± 15.5 years, ranging from 18 to 85 years, the median was 35.5 years. More than one third (34.4%) aged <30 years. More than half (56.7%) were male, and the male: female ratio was 1.3:1 as presented

**Table 1: Sociodemographic characteristics**

| | *n* (%) |
|---|---|
| Age at presentation (years) | |
| <30 | 31 (34.4) |
| 30-39 | 21 (23.3) |
| 40-49 | 18 (20.0) |
| ≥50 | 20 (22.2) |
| Mean±SD | 37.5±15.5 |
| Gender | |
| Male | 51 (56.7) |
| Female | 39 (43.3) |
| Address | |
| Erbil | 38 (42.2) |
| Other governorates | 52 (57.8) |
| Residency | |
| Urban | 62 (68.9) |
| Rural | 28 (31.1) |
| Total | 90 (100.0) |

SD=Standard deviation

in Table 1, which shows that 57.8% of the patients were living outside Erbil and 68.9% were living in urban areas [Table 1].

Most of our patients (91%) represented the classical (hypergranular) APL subtype versus 9% for the hypogranular variant. The majority of the patients presented with more than one sign and symptom where 71.4% of the patients presented with generalized weakness, 64.44% presented with bleeding, 48.9% presented with fever, and only 2.2% presented with thrombosis. Regarding the method of diagnosis, morphological examination of peripheral blood and bone marrow with immunochemical stains was done for all the patients, cytogenetics was done for 14 (15.6%) patients, and flow cytometry was done for those 14 patients in addition to another 25 patients, so the total was 39 patients (43.3%) as presented in Table 2. The means, minimum, and maximum values of the patients' blood indices are presented in Table 3.

As mentioned, 90 patients with APL presented to the hospital, six of them left the hospital before starting the management plan, and 18 patients died in the hospital before starting the chemotherapy, so what is left is 66 patients (received chemotherapy). More than two thirds (68.2%) of those 66 patients achieved CR, but 14 patients of them (31.1%) relapsed later on as presented in Table 4 which shows that 50 patients out of the 84 patients (59.5%) died at the end of the study.

The mean time of achieving CR in those patients who did not relapse was 32.9 days in comparison to 39.5 days in the relapsed category ($P = 0.172$).

The main reasons of mortality were infection (36%), bleeding (28%), DS (14%), and respiratory failure (10%), in addition to the other causes mentioned in Table 5. Regarding time of death, 18 patients (36% of the dead patients) died before starting chemotherapy, 21 (42%) died during induction chemotherapy, 2 (4%) died during consolidation therapy, and the remaining 9 patients (18%) died during relapse. Hence, 11 patients achieved CR and died later on (8 due to infections and 3 due to bleeding complications), the mean time between CR and death was 467 days.

Table 6 shows that 39 patients (out of 84 patients) died early (prior or during induction chemotherapy). The factors found to be significantly associated with early death were risk score and WBC count. The more the risk score, the higher the rate of early death where it is evident that the rate was 58.1% among those with high risk ($P = 0.006$). The early death rate was high (58.1%) among those with WBC count of more than $10 \times 10^9$/L, compared with 34.4% among those with WBC count of $\leq 10 \times 10^9$/L ($P = 0.028$). No significant association was detected between early death rate with age ($P = 0.690$), gender ($P = 0.899$), hemoglobin ($P = 0.115$), and platelets ($P = 0.128$).

**Table 2: Clinical presentation and method of diagnosis**

| | *n* (%) (*n*=90) |
|---|---|
| Clinical presentation | |
| Generalized weakness | 64(71.14) |
| Bleeding | 58(64.44) |
| Fever | 44(48.90) |
| Thrombosis | 2(2.24) |
| Method of diagnosis | |
| Morphology | 90(100) |
| Flowcytometry | 39(43.3) |
| Cytogenetics | 14(15.6) |

**Table 3: Laboratory presentation**

| | Value (mean+SD) | Minimum | Maximum |
|---|---|---|---|
| PT, seconds | 17.282±2.843 | 10.6 | 28 |
| PTT, seconds | 28.750±5.265 | 19 | 55 |
| INR | 1.3802±0.325 | 0.8 | 2.8 |
| WBC, cell* $10^9$/L | 22.373±29.498 | 0.4 | 123 |
| Platelets, cell* $10^9$/L | 33.378±27.511 | 1 | 124 |
| Hb, g/dl | 8.317±2.698 | 3.5 | 14.6 |

SD=Standard deviation

**Table 4: Progress and outcome of patients**

| | *n* (%) |
|---|---|
| Complete remission (*n*=66)* | |
| No | 21 (31.8) |
| Yes | 45 (68.2) |
| Relapse (*n*=45) | |
| No | 31 (68.9) |
| Yes | 14 (31.1) |
| Status at the end (*n*=84) | |
| Alive | 34 (40.5) |
| Dead | 50 (59.5) |

*Six patients were missing and 18 patients died before starting treatment

**Table 5: Causes and time of death**

| | *n* (%) |
|---|---|
| Causes of death | |
| Infection | 18 (36.0) |
| Bleeding* | 14 (28.0) |
| Differentiation syndrome | 7 (14.0) |
| Respiratory failure | 5 (10.0) |
| Acute renal failure | 2 (4.0) |
| Pulmonary embolism | 2 (4.0) |
| Ischemic CVA | 1 (2.0) |
| Liver failure | 1 (2.0) |
| Time of death | |
| Prior to treatment | 18 (36.0) |
| Induction chemotherapy | 21 (42.0) |
| Consolidation | 2 (4.0) |
| Relapse | 9 (18.0) |
| Total | 50 (100.0) |

*The site of bleeding was central nervous system (7 patients), pulmonary (3 patients), gastrointestinal tract (3 patients), and vaginal bleeding (1 patient). CVA=Cerebrovascular accident

Figure 1 and Table 7 show significant differences in the mean survival times of patients classified according to the risk scores into low, intermediate, and high risk.

**Table 6: Rate of early death by several factors**

| | *n* | Early death, *n* (%) | Degree of freedom | *P* |
|---|---|---|---|---|
| Age (years) | | | | |
| <30 | 31 | 12 (38.7) | 3 | 0.690 |
| 30-39 | 20 | 10 (50.0) | | |
| 40-49 | 17 | 8 (47.1) | | |
| ≥50 | 16 | 9 (56.3) | | |
| Gender | | | | |
| Male | 48 | 22 (45.8) | 1 | 0.899 |
| Female | 36 | 17 (47.2) | | |
| Risk | | | | |
| Low | 13 | 1 (7.7) | 2 | 0.006 |
| Intermediate | 28 | 13 (46.4) | | |
| High | 43 | 25 (58.1) | | |
| Hb (g/dl) | | | | |
| ≤10 | 67 | 34 (50.7) | 1 | 0.115 |
| >10 | 17 | 5 (29.4) | | |
| WBCs | | | | |
| ≤10 | 41 | 14 (34.1) | 1 | 0.028 |
| >10 | 43 | 25 (58.1) | | |
| Platelets | | | | |
| ≤40 | 60 | 31 (51.7) | 1 | 0.128 |
| >40 | 24 | 8 (33.3) | | |
| Total | 84 | 39 (46.4) | | |

WBCs=White blood cells

**Table 7: Mean survival time by risk categories**

| Risk | Mean survival time in days | | | | *P** |
|---|---|---|---|---|---|
| | Estimate | SE | 95% CI | | |
| | | | Lower bound | Upper bound | |
| Low | 1977.31 | 216.15 | 1553.64 | 2400.97 | 0.001 |
| Intermediate | 1625.16 | 317.70 | 1002.47 | 2247.85 | |
| High | 822.41 | 212.99 | 404.95 | 1239.88 | |
| Overall | 1392.59 | 182.76 | 1034.38 | 1750.80 | |

*By log rank (Mantel-Cox). SE=Standard error, CI=Confidence interval

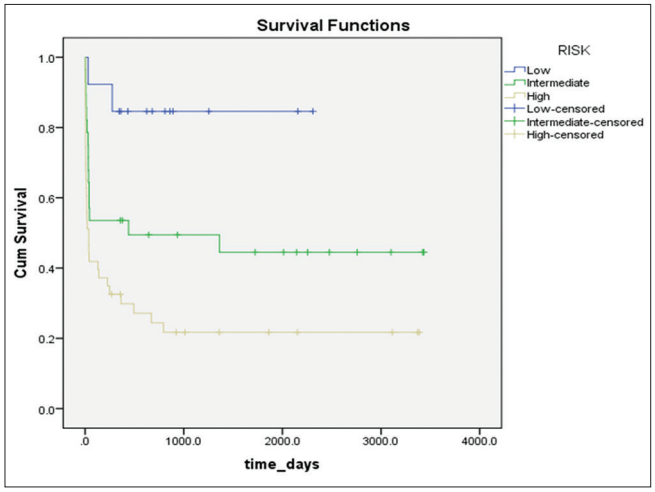


**Figure 1:** Survival curve according to risk categories

Table 6 shows that the higher the risk, the less the mean survival time which was 1977.31 days among those with low risk and 822.41 days among those with high risk ($P$ = 0.001). The 5-year survival rate was 37.8% as shown in Figure 2.

## Discussion

Based on our information, this maybe the first record from Iraq outlining a 10-year practice concerning APL. No considerable difference from preceding data was noticed in regard to demographics. Young age at presentation is a frequent finding, the median age is around 30s. Our study revealed similar results to those done by Sanz *et al*.[14] and Mandelli *et al*.[15] regarding median age. Until now, no sex prediction was expressed in the former epidemiological reviews, also our study showed the same.[6,16-18] Most of our patients were from the urban area, a finding that is supported by large multicenter study of 1400 APL patients.[19]

Typically, patients were symptomatic at time of presentation to the hospital, usually bleeding, fever, fatigue, or those with thrombosis. In our study, the main presenting symptom was generalized weakness (71%) and bleeding was reported in 64.4% of the patients, a finding that is slightly lower in those researches described from New Delhi (69.7%), Cairo (79%), and Abu Dhabi (81%).[17,20-22] In agreement with previous reports,[17,23] half of our patients presented with fever. The incidence of thrombotic events ranged from 2% to 10% in previous reviews,[24,25] in our group, it was 2.2%. Hence, the clinical presentations of our patients are comparable to the published articles.

Referral delay of the majority of our patients may explain the finding of having more than half of them to the high-risk group in comparison to 20%–40% in many

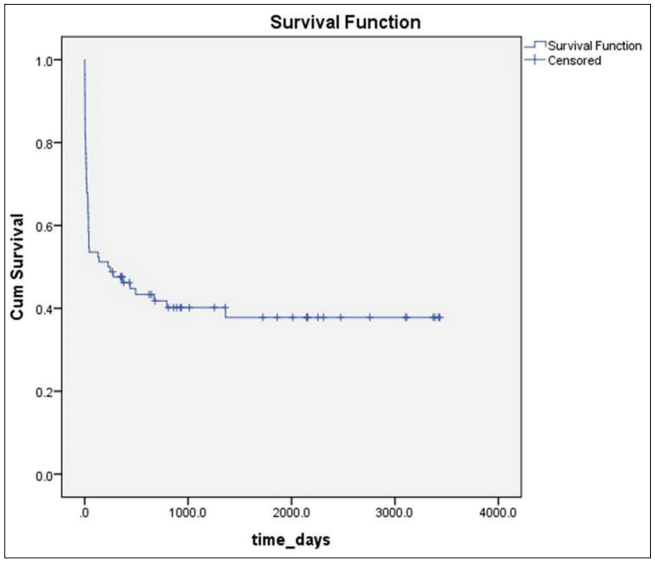


**Figure 2:** Overall survival

previous reports, as most of our patients were living outside Erbil city.[16,22,23,26-29] Deficient understanding for the disease seriousness by the patients, financial issues, and the general practitioners may not assume the diagnosis early, all justify presenting late.

Regardless of the progress in outcome of APL, early death presents the main causative factor for treatment failure. Early death rates between patients with APL testified in the literature vary widely, a Turkish study reported a high incidence of early death at 40%,[30] 32% was reported in a Brazilian study,[31] and a Greek study found the rate to be 14.9%[28] and 61% in Pakistan,[8] and 14.6% in a Tunisian study.[32] Here, we report early death of 46% among our patients which is on the high side in comparison with the mentioned studies. The probable explanation for the high early mortality is possibly attributable to the high percentage of high-risk category in our study; another explanation could be the delay in referral of the patients which consequently delayed the administration of ATRA and supportive treatment. In agreement with previous reports, elevated WBC count and high-risk score associated with high rates of early mortality.[26,33-39]

This study showed the lower CR rates and overall survival and higher rate of relapse in comparison with other reports.[16,20,23,32,40,41] Many factors contributed to these findings; the high number of high-risk patients, the high early mortality rate, the high incidence of infections along with inaccessibility to highly specialized microbiological laboratories, in addition to the unavailability of ATO in our area in most of the study period. Molecular evaluation (detection of minimal residual disease and molecular relapse) have been shown an important tool in guiding further therapy and early treatment of molecular proven relapse showed better results than waiting until morphological relapse,[42] those techniques were not available in our center and blamed to be one of the causes of late intervention and higher mortality.

A significant association between the overall survival and risk score had been shown in our study, prognosis among patients who are in the high-risk group is typically expected to be bad. Similar results were reported by other international studies.[8,23,36,43,44]

Regarding the causes of death in our study, infections were the main cause of death followed by bleeding, in contrast with other studies which showed hemorrhage as the main cause of death.[8,11,23,30,45,46] Late presentation to the hospital and delayed receiving treatment, absence of isolation rooms in our center, lack of accurate microbial cultures, and inability of most of our patients to afford expensive drugs like antifungals are likely explanations for the high percentage of infections. Hence, early diagnosis, prompt treatment with standard chemotherapy protocols, more intensive support treatment including early access to facilities for treatment and prevention of coagulopathy, and early recognition and treatment of DS is therefore essential in improving survival of APL patients. The most common hemorrhagic sites in our patients are the brain and lung, which is similar to other studies.[39,45,47]

## Conclusion

The conclusions were drawn from our retrospective study; the clinical and epidemiological features were comparable with previously published studies. High-risk patients predominate in our study population. Early mortality rate was very high, high WBC count on presentation, and high-risk score were significant predictors. Mortalities were mostly due to infections, hemorrhagic events, and DS. Despite the remarkable improvement in the therapeutics of APL, the overall survival in our center is still low as high-risk patients have significant higher risk of mortality.

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### Conflicts of interest
There are no conflicts of interest.

## References

1. Szotkowski T, Faber E, Hubacek J, Raida L, Rohon P, Kuba A, *et al*. Acute promyelocytic leukemia successfully treated also in elderly patients with significant comorbidities: A 20-year single-center experienc. Neoplasma 2015;62:146-51.
2. Ahn S, Park JS, Jeong SH, Lee HW, Park JE, Kim MH, *et al*. Current routine practice and clinico-pathological characteristics associated with acute promyelocytic leukemia in Korea. Blood Res 2013;48:31-4.
3. Sultan S, Irfan SM, Ashar S. Acute Promyelocytic Leukemia: A Single Center Study from Southern Pakistan. Asian Pac J Cancer Prev 2015;16:7893-5.
4. Baljevic M, Park JH, Stein E, Douer D, Altman JK, Tallman MS. Curing all patients with acute promyelocytic leukemia: are we there yet? Hematol Oncol Clin North Am 2011;25:1215-33, viii.
5. Rego EM, Jacomo RH. Epidemiology and treatment of acute promyelocytic leukemia in latin america. Mediterr J Hematol Infect Dis 2011;3:e2011049.
6. Mele A, Stazi MA, Pulsoni A, Visani G, Monarca B, Castelli G, *et al*. Epidemiology of acute promyelocytic leukemia. Haematologica 1995;80:405-8.
7. Choudhry A, DeLoughery TG. Bleeding and thrombosis in acute promyelocytic leukemia. Am J Hematol 2012;87:596-603.
8. Karim F, Shaikh U, Adil SN, Khurshid M. Clinical characteristics, outcome and early induction deaths in patients with acute promyelocytic leukaemia: a five-year experience at a tertiary care centre. Singapore Med J 2014;55:443-7.
9. Asou N, Adachi K, Tamura U, Kanamaru A, Kageyama S, Hiraoka A, *et al*. Analysis of prognostic factors in newly diagnosed

patients with acute promyelocytic leukemia: the APL92 study of the Japan Adult Leukemia Study Group (JALSG). Cancer Chemother Pharmacol 2001;48 Suppl 1:S65-71.

10. Daver N, Kantarjian H, Marcucci G, Pierce S, Brandt M, Dinardo C, *et al*. Clinical characteristics and outcomes in patients with acute promyelocytic leukaemia and hyperleucocytosis. Br J Haematol 2015;168:646-53.
11. Crespo-Solis E, Contreras-Cisneros J, Demichelis-Gomez R, Rosas-Lopez A, Vera-Zertuche JM, Aguayo A, *et al*. Survival and treatment response in adults with acute promyelocytic leukemia treated with a modified International Consortium on Acute Promyelocytic Leukemia protocol. Rev Bras Hematol Hemoter 2016;38:285-90.
12. Chen C, Huang X, Wang K, Chen K, Gao D, Qian S. Early mortality in acute promyelocytic leukemia: Potential predictors. Oncol Lett 2018;15:4061-9.
13. Breccia M, Latagliata R, Cannella L, Minotti C, Meloni G, Lo-Coco F. Early hemorrhagic death before starting therapy in acute promyelocytic leukemia: association with high WBC count, late diagnosis and delayed treatment initiation. Haematologica 2010;95:853-4.
14. Sanz MA, Lo Coco F, Martin G, Avvisati G, Rayon C, Barbui T, *et al*. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood 2000;96:1247-53.
15. Mandelli F, Diverio D, Avvisati G, Luciano A, Barbui T, Bernasconi C, *et al*. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups. Blood 1997;90:1014-21.
16. Yildirim R, Gundogdu M, Ozbicer A, Kiki I, Erdem F, Dogan H. Acute promyelocytic leukemia, centre, experience, Turkey. Transfus Apher Sci 2013;48:45-9.
17. Hassan IB, Zaabi MRA, Alam A, Hashim MJ, Tallman MS, Kristensen J. Characteristics features and factors influencing early death in Acute promyelocytic leukemia; Experience from United Arab Emirates (UAE). Int J Hematol 2017;106:90-8.
18. Dayama A, Dass J, Seth T, Mahapatra M, Mishra PC, Saxena R. Clinico-hematological profile and outcome of acute promyelocytic leukemia patients at a tertiary care center in North India. Indian J Cancer 2015;52:309-12.
19. Park JH, Qiao B, Panageas KS, Schymura MJ, Jurcic JG, Rosenblat TL, *et al*. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood 2011;118:1248-54.
20. Bajpai J, Sharma A, Kumar L, Dabkara D, Raina V, Kochupillai V, *et al*. Acute promyelocytic leukemia: an experience from a tertiary care centre in north India. Indian J Cancer 2011;48:316-22.
21. Avvisati G, Lo Coco F, Diverio D, Falda M, Ferrara F, Lazzarino M, *et al*. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. Blood 1996;88:1390-8.
22. Khorshid O, Diaa A, Moaty MA, Fatah RA, Dessouki IE, Hamid MA, *et al*. Clinical features and treatment outcome of acute promyelocytic leukemia patients treated at cairo national cancer institute in egypt. Mediterr J Hematol Infect Dis 2011;3:e2011060.
23. Rego EM, Kim HT, Ruiz-Arguelles GJ, Undurraga MS, Uriarte Mdel R, Jacomo RH, *et al*. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. Blood 2013;121:1935-43.
24. Mitrovic M, Suvajdzic N, Elezovic I, Bogdanovic A, Djordjevic V, Miljic P, *et al*. Thrombotic events in acute promyelocytic leukemia. Thromb Res 2015;135:588-93.
25. Chang H, Kuo MC, Shih LY, Wu JH, Lin TL, Dunn P, *et al*. Acute promyelocytic leukemia-associated thrombosis. Acta Haematol 2013;130:1-6.
26. Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Mollgard L, *et al*. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia 2011;25:1128-34.
27. Ades L, Sanz MA, Chevret S, Montesinos P, Chevallier P, Raffoux E, *et al*. Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French-Belgian-Swiss and PETHEMA results. Blood 2008;111:1078-84.
28. Pagoni M, Garofalaki M, Panitsas F, Manola K, Psarra K, Economopoulos P, *et al*. Acute promyelocytic leukemia: an experience on 95 greek patients treated in the all-trans-retinoic Acid era. Mediterr J Hematol Infect Dis 2011;3:e2011053.
29. Rashidi A, Riley M, Goldin TA, Sayedian F, Bayerl MG, Aguilera NS, *et al*. Delay in the administration of all-trans retinoic acid and its effects on early mortality in acute promyelocytic leukemia: final results of a multicentric study in the United States. Leuk Res 2014;38:1036-40.
30. Serefhanoglu S, Buyukasik Y, Goker H, Sayinalp N, Haznedaroglu IC, Aksu S, *et al*. Clinical features and outcomes of 49 Turkish patients with acute promyelocytic leukemia who received ATRA and anthracyclines (PETHEMA protocol) therapy. Leuk Res 2010;34:e317-9.
31. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Woods WG, *et al*. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. Blood 2002;100:4298-302.
32. Jeddi R, Ghedira H, Menif S, Ben Neji H, Ben Amor R, Kacem K, *et al*. Treatment of acute promyelocytic leukemia with PETHEMA LPA 99 protocol: a Tunisian single center experience. Hematology 2010;15:204-9.
33. Xu F, Wang C, Yin C, Jiang X, Jiang L, Wang Z, *et al*. Analysis of early death in newly diagnosed acute promyelocytic leukemia patients. Medicine (Baltimore) 2017;96:e9324.
34. Zhao H, Zhao Y, Zhang Y, Hou J, Yang H, Cao F, *et al*. Difference in causes and prognostic factors of early death between cohorts with de novo and relapsed acute promyelocytic leukemia. Ann Hematol 2018;97:409-16.
35. Lou Y, Ma Y, Sun J, Suo S, Tong H, Qian W, *et al*. Effectivity of a modified Sanz risk model for early death prediction in patients with newly diagnosed acute promyelocytic leukemia. Ann Hematol 2017;96:1793-800.
36. Park S, Lee SJ, Kim K, Jang JH, Kim DH, Lee KH, *et al*. Inclusion of hemoglobin level in prognostic score provides better prognostic stratification in patients with acute promyelocytic leukemia (APL). Int J Hematol 2013;97:388-96.
37. Liu YJ, Wu DP, Liang JY, Qiu HY, Jin ZM, Tang XW, *et al*. Long-term survey of outcome in acute promyelocytic leukemia: a single center experience in 340 patients. Med Oncol 2011;28 Suppl 1:S513-21.
38. Testa U, Lo-Coco F. Prognostic factors in acute promyelocytic leukemia: strategies to define high-risk patients. Ann Hematol 2016;95:673-80.
39. Breccia M, Lo Coco F. Thrombo-hemorrhagic deaths in acute promyelocytic leukemia. Thromb Res 2014;133 Suppl 2:S112-6.
40. Xin L, Wan-jun S, Zeng-jun L, Yao-zhong Z, Yun-tao L, Yan L, *et al*. A survival study and prognostic factors analysis on acute promyelocytic leukemia at a single center. Leuk Res 2007;31:765-71.
41. Hessenauer MR, Farhadfar N, Gangat N. Incidence and Management of Relapsed Acute Promyelocytic Leukemia. Blood. 2016;128:5179.
42. Coco FL, Diverio D, Falini B, Biondi A, Nervi C, Pelicci PG. Genetic Diagnosis and Molecular Monitoring in the Management of Acute

Promyelocytic Leukemia. Blood. 1999;94:12-22.
43. Coutre S. Classification and risk stratification for acute promyelocytic leukemia. Clin Lymphoma Myeloma Leuk. 2010;10 Suppl 3:S127-9.
44. Jacomo RH, Melo RA, Souto FR, de Mattos ER, de Oliveira CT, Fagundes EM, *et al*. Clinical features and outcomes of 134 Brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines. Haematologica. 2007;92:1431-2.
45. Chang H, Kuo MC, Shih LY, Dunn P, Wang PN, Wu JH, *et al*. Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia. Eur J Haematol 2012;88:321-8.
46. Rogers JE, Yang D. Differentiation syndrome in patients with acute promyelocytic leukemia. J Oncol Pharm Pract 2012;18:109-14.
47. Yanada M, Matsushita T, Asou N, Kishimoto Y, Tsuzuki M, Maeda Y, *et al*. Severe hemorrhagic complications during remission induction therapy for acute promyelocytic leukemia: incidence, risk factors, and influence on outcome. Eur J Haematol. 2007;78:213-9.