<u>**Original Article**</u>

Acute Promyelocytic Leukemia in Children: A Single Centre Experience from Turkey

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Abstract. *Background and objectives:* **Acute promyelocytic leukemia (APL), is a distinct subtype of acute myeloid leukemia (AML) characterized by a tendency to hemorrhage and excellent response to all-trans retinoic acid (ATRA). In this retrospective study, we aimed to determine the incidence, clinical symptoms, toxicities, and outcome of children with APL in our center.** *Methods***: We retrospectively reviewed the medical records of children (age < 18 years) diagnosed with APL in our pediatric hematology department between January 2006-December 2016.**
Results: **Pediatric APL represents 20.5% of AML cases in this cohort. Most of the cases presented as classical M3, albeit hypogranular variant was described in 12% of the cohort. Patients with hypogranular variant APL were differed from classical APL by co-expression of CD2 and CD34. About ¾ of APL patients had hemorrhagic findings at admission or the induction treatment. Severe bleeding manifested as intracranial hemorrhage was present in three patients and intracranial arterial thrombosis was present in one. Six patients showed side effects of ATRA such as pseudotumor cerebri, differentiation syndrome resulting in dilated cardiomyopathy, and pulmonary infiltrates. Five-year overall survival (OS) and early death rate were found to be 82.5% and 12% respectively.**
Conclusions: **A high frequency (20.5%) of APL was noted among children with AML in this single-center study. The overall mortality rate was 17.5%. Since the induction death rate was 12% and life-threatening bleeding was the primary problem, awareness and urgent treatment are critical factors to reduce early losses.**

Keywords: Acute promyelocytic leukemia, Hypogranular variant APL, ATRA toxicity.

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Introduction. Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) which is classified as M3 by French-American-British (FAB) Cooperative group.[1] The incidence of APL among the AML cases in children and adolescents vary from 2% in Switzerland to >50% in Nicaragua.[2] However, APL incidence among eastern Mediterranean countries is not well documented. A multicenter study from Lebanon reported 25% APL cases among AML patients.[3] In Turkey, a study

disclosed an incidence of APL as 8.8% among 34 AML patients at childhood.[4]

Acute promyelocytic leukemia is characterized by the presence of reciprocal translocation between chromosomes 15 and 17 [t(15;17); promyelocytic leukemia gene (PML) - retinoic acid receptor gene alpha (RARA) fusion].[5,6] In addition to PML, rare partner genes such as nucleophosmin (NPM1; 5q35), nuclear mitotic apparatus protein 1 (NUMA1; 11q13), promyelocytic leukemia zinc finger (PLZF; 11q23), and signal transducer and activator of transcription (STAT) 5β (STAT5b; 17q21) have been defined.[7] PML-RARA fusion protein impairs differentiation of the myeloid progenitor cells and leads to arrested maturation at the promyelocytic stage. By binding to the PML-RARA fusion protein, ATRA induces differentiation of leukemic cells into mature granulocytes and ultimately apoptosis.[8,9] Coagulopathy and signs of clinical hemorrhage or thrombotic complications and an excellent response to all-trans retinoic acid (ATRA) are distinctive features of APL.[10] Anthracycline-based chemotherapy and ATRA combination are curative for at least 80% of newly diagnosed APL patients.[10,11,12] Arsenic trioxide (ATO) initially was introduced into the treatment of relapsed APL. Subsequently, it was used as first-line APL therapy, which can achieve remission rates of 86%.[13,14,15]

Here, we report clinical, and laboratory findings, toxicities of ATRA treatment and outcome of APL patients, followed in our department.

Materials and Methods. We retrospectively reviewed the medical records of children (age < 18 years) diagnosed with AML in our pediatric hematology department between January 2006-December 2016. Demographic, clinical, and laboratory data (hematological and biochemical findings; bone marrow morphology, immune phenotype, chromosomal and cytogenetic analysis; radiologic and echocardiographic findings), chemotherapy protocols, toxicities and the prognosis of the children were recorded for all APL patients. Morphologic diagnosis of APL was based on FAB criteria.[1]Leukemic cells were analyzed by flow cytometry, and the diagnosis was confirmed by the presence of t(15;17) with fluorescence in situ hybridization (FISH) analysis. Patients were treated according to APL-93 trial,

GIMEMA-AIEOP AIDA between 2006-2010 and AML-BFM Interim 2004 therapy protocol between 2011-2016.[11,16,17] ATRA courses were used in all protocols with a dose of 25 to 45 mg/m^2/d from the induction to during with maintenance treatment. Maintenance treatment was planned for 1 to 2 years in AML-BFM 2004, APL-93 and AIDA protocols. However, none of the regimens included ATO. Complete remission was defined according to the report of the National Cancer Institute workshop criteria.[18] Cytogenetic remission using FISH analysis was defined as the disappearance of the t(15;17). Early death was defined as the death of any cause within 30 days of admission.[19] The overall survival (OS) was calculated from the date of diagnosis to death of any cause or last follow-up. ATRA related adverse effects such as fever, weight gain, dyspnea, interstitial pulmonary infiltrate, hypotension, renal insufficiency, and hyperbilirubinemia was also recorded as differentiation syndrome (DS) which was defined according to Frankel et al.[20]

Statistical analysis. Statistical analysis was performed by using Statistical Package for the Social Sciences for Windows (SPSS) version 18.0 (SPSS Inc., South Wacker Drive, Chicago, IL, USA). The variables were investigated using visual and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed and median and minimum-maximum for non-normally distributed variables. The overall survivals of APL patients were calculated using the Kaplan–Meier methods and the log-rank test.

Results. Between January 2006 - December 2016, 83 children diagnosed with AML at our center. Among them, 17 patients (20.5%) with newly diagnosed APL were included in the study. Eight girls and nine boys [median age 13.5 years (range 1.5-17)] were included in the study. Pretreatment laboratory findings and detailed characteristics of the patients are reported in T**able 1** and **Table 2**.

Bleeding (76.5%), fever (58.8%), and fatigue (47%) were the most common presenting signs and symptoms. Bone pain and a headache were seen in four and three patients. Bleeding was cutaneous in 6, and mucosal (e.g., wet purpura,

Table 1. Pretreatment laboratory characteristics of the patients

Complete blood counts	Median	Range
Hemoglobin, g/dL	8.7	4.7-13.4
WBC, x10³/µL	4	1-23.1
High-risk⁺ n= (%)	4 (23.5)	
Low-intermediate-risk⁺ n= (%)	13 (76.5)	
Platelet, x10³/µL	21	4-209
Circulating blasts, %*	38	0-100%
Fibrinogen level, g/L	149.5	73-505

⁺ Patients with Sanz high risk (WBC >/= 10 x10³/µ) versus low-intermediate risk (WBC <10 x10³/µL). *Data missing for 4 patients.

Table 2. Detailed data of the patients.

Patient no	Age (year)	Sex	Diagnosis	WBC (x10³/µL)	PB blast (%)	Treatment protocol	ATRA toxicity	Complications	Follow-up (month)	Outcome
1	8.5	F	M3v	10.8	76	AML BFM 2004	PTC		62	Alive
2*	9	F	M3	23.1	100	APL-93	DS (Pancarditis, dilated cardiomyopathy)		101	Alive
3	3.2	M	M3	1.7	N/A	AIDA	PTC		91	Alive
4	15	M	M3	2.8	100	APL-93		Retinal hemorrhage	105	Alive
5	17	M	M3	5.6	12	AML BFM 2004		None	32	Alive
6	6	F	M3v	7.8	56	AIDA		None	103	Alive
7	13.5	M	M3	7.3	22	AIDA		None	105	Alive
8	14	M	M3	3.6	60	AIDA	DS (Pulmonary infiltrates)	Cholecystitis – Pancreatitis	25	Alive
9	1.5	M	M3	11.2	14	AML BFM 2004		None	69	Alive
10	10	M	M3	1	0	AIDA		None	106	Alive
11	16	F	M3	1	N/A	AIDA		None	97	Alive
12	14	M	M3	1.8	10	AIDA	DS	ICH, ARF, pulmonary edema	11 days	Died, ICH
13	14	F	M3	2.7	50	AML BFM 2004	PTC	ICH	46	Alive
14	6	F	M3	10.9	100	AML BFM 2004		None	47	Alive
15	7.5	M	M3	4	N/A	AML BFM 2004		Left MCA thrombosis	20	Alive
16	15.3	F	M3	2.6	58	AML BFM 2004		ICH	4 days	Died, ICH
17*	14	F	M3	2.3	N/A	AIDA		ARF + Sepsis	4	Died, Sepsis

ARF=Acute renal failure; ATRA=All-trans retinoic acid; DS=Differentiation syndrome; ICH=Intracranial hemorrhage; MCA=Middle cerebral artery; N/A=Not available; PB=Peripheral blast; PTC=Pseudotumor cerebri;*Published before.

epistaxis, and gingival bleeding) in 7 patients. Furthermore, hematuria, hemoptysis, and retinal hemorrhage were presented, each in one patient. Intracranial hemorrhage (ICH) was demonstrated in three patients; one of them at admission and two others were during 11th and 23rd days of induction treatment. The patient who had ICH demonstrated 23rd days of induction had coagulopathy at admission that recovered with ATRA treatment. Unfortunately, subacute/chronic subdural hematoma with midline shift was revealed while she had a neutropenic fever period with thrombocytopenia. One patient who initially diagnosed with left middle cerebral artery thrombosis, diagnosed with APL on the 5th day of admission. Organomegaly was present in seven (41%) patients, including splenomegaly in five and hepatomegaly in five patients. Additionally, lymphadenopathy or central nervous involvement detected in one patient each.

Median hemoglobin, white blood cell (WBC) and platelet counts were summarized in **Table 1**.

Patients reclassified with Sanz high-risk (WBC ≥ 10 x10^3/µL) versus low-intermediate-risk (WBC <10 x10^3/µL) in **Table 1**.[21] Peripheral blasts were presented in 16 (94%) of 17 patients at admission. Fourteen patients (82%) had coagulopathy (increased PT, aPTT, and decreased fibrinogen levels). D-dimer levels were elevated in the 11 of the 15 patient.

Fifteen patients (88%) had classical FAB M3 type blasts at bone marrow morphology; two patients (12%) had M3v blasts which was estimated by morphology and then confirmed by flow cytometric findings. Blasts of 15 patients who had classical hypergranular APL were positive for CD117, CD13, CD33 markers. Out of 15, three patients' blasts were positive for CD34 and/or HLA DR. But, flow cytometric analysis of 2 patients with M3v APL differed from classical APL by co-expression of CD2 and CD34 in addition to CD117, CD13. Meanwhile, CD2 expression was present at a low level (24%) in only one patient with classical M3. All of the patients had t(15;17) by FISH analysis, and three patients (18%) had hypodiploid karyotype as well. Fifteen patients (88%) achieved complete remission. Mean morphologic remission and complete cytogenetic remission intervals were 30.4 ± 9.1 days (15-45 days) and 51.7 ± 19.6 days (26-98 days), respectively. There were no relapses during the entire follow-up period through June 2017 (follow-up range: 10-106 months). Two patients died at the induction before hematological response achieved. The induction death rate and the overall mortality were 12% and 17.5%, respectively. One of them, a 15-year old girl who admitted in a coma with massive ICH. Her history revealed that she had been followed 72 hours in a local hospital before diagnosis. Unfortunately, despite ATRA and supportive treatment, she died at day 4 of admission to our hospital. We suggested that delay in the ATRA treatment that caused ICH was the main cause of death. Another patient, a 14-year old boy died due to acute renal failure, pulmonary edema, and ICH at day 11 of induction treatment. Though DS was suggested, sepsis and DIC were the additional causative factors that ultimately caused death. Additionally, a 14-year-old girl died due to sepsis four months after the diagnosis. After excluding these three patients, median follow up period of the patients was 69 months (range 10 – 106). Estimated 5-year overall survival rate was 82.5 ± 9.1 (95 CI: 64.7 – 100.4).

Several complications were detected during APL treatment (**Table 2**). Three patients (18%) developed pseudotumor cerebri (PTC); one of them diagnosed at the fifth month, at the early phase of maintenance therapy. She treated with topiramate and repeated lumbar punctures. The second patient developed PTC 10 months after APL diagnosis while receiving maintenance treatment. He was treated with acetazolamide and serial lumbar punctures. The last patient developed PTC 45 days after diagnosis of APL and treated with acetazolamide, serial lumbar punctures, and dexamethasone. A 14-y-old boy developed pulmonary infiltrates, tinnitus and hypotension on the sixth day of induction treatment, diagnosed with DS, responded to dexamethasone. Additionally, he suffered from cholecystitis and pancreatitis at the second month of APL treatment. A previously described 9-year old girl from our department who developed endocarditis and myocarditis at the induction of the APL treatment, recovered after cessation of ATRA who has been reported elsewhere.[22] However, readministration of ATRA at the maintenance therapy caused pancarditis and severe pulmonary edema that might have been part of DS, which recovered with corticosteroids treatment and discontinuation of ATRA. Unfortunately, she developed dilated cardiomyopathy and still ongoing with digitalis treatment. The clinical picture strongly suggested the ATRA treatment as the causative factor even if anthracyclines were an additional risk factor. Febrile neutropenia has been observed during induction treatment in 15 patients (88%), including septicemia and typhilitis. Median febrile neutropenia attack rate was 3.5 (range 1-7) during the treatment period.

Discussion. Pediatric APL represents 20.5% of AML cases in our cohort. Even if our center is a reference hospital in Ankara, this high incidence of APL needs to be confirmed in larger pediatric series among Turkey. Early diagnosis and immediate treatment with ATRA may reduce hemorrhagic complications that lead to early morbidity and mortality, and significant concern is discrimination of APL from other subtypes of AML. In our patients whose presenting, symptoms are bleeding and/or coagulopathy, expeditious immunophenotypic analysis to exclude M3 or

M3v is performed. We started ATRA as soon as possible, although two patients experienced ICH after the first week of ATRA. Unfortunately, delays in diagnosis contributed to mortality in one of the patient. However, favorable response to ATRA has been achieved in the rest of the patients. Morphology and immunophenotypic analysis are still essential tools for rapid recognition of APL. Most of our APL cases presented as hypergranular or classical M3, albeit morphological hypogranular or microgranular variant type, M3v, was also described in 2 patients (12%). Hypogranular variant type accounts for 15- 20% of APL cases which is characterized by promyelocytes with bilobed-multilobed or angel wing shaped nucleus look as if monoblastic leukemia.[8,23] On both occasions, identification of the cytogenetic abnormality, t(15;17) or PML/RARA translocation has utmost importance. M3v morphology is not diagnostic; however, co- expression of CD2 and CD34 markers are remarkable and useful for early diagnosis.[24,25] The absence of HLA-DR, low expression or absence of CD34, and positivity for CD13 and/or CD33 markers has been reported on both forms.[24,25] In our cohort, fifteen patients (88%) expressed CD117, CD13, CD33 markers. They did not express CD34 and/or HLA-DR except for three cases (17.5%) who diagnosed with APL ultimately. Two patients with hypogranular variant were differed from classical APL by co-expression of CD2 and CD34 (100%) in this study.

APL cases were frequently presented with consumptive coagulopathy that may cause life-threatening hemorrhages.[26] Furthermore, thrombotic complications may also be seen infrequently.[26] About ¾ of our APL patients had hemorrhagic findings at admission or induction treatment. Severe bleeding manifested as intracranial hemorrhage was present in three patients. One of them admitted with severe ICH, but we demonstrated ICH in two patients after the first week of ATRA treatment. The other patient who had bleeding on day 11 of induction, had been diagnosed with sepsis and DIC, and also possible DS. Patients with ICH has been supported with aggressive platelet and fibrinogen replacement along with ATRA therapy guided by numerous coagulation studies. ATRA has dramatically enhanced survival rates and diminished relapse rates in APL patients. In the present study, five-year overall survival (OS) and

early death rate were found to be 82.5% and 12%, respectively. ATRA resistance and relapse were not observed in any patient. Our results were comparable to those obtained in population-based studies and also to early death rates for APL.[27,28] Nevertheless, Abla et al.[19] reported the incidence of early death as 4.7%, recently.

High WBC, high peripheral blast count, M3v and black ethnicity were independent predictors of early hemorrhagic death in several studies.[19,29] However, our patients who died due to early ICH had low WBC counts (1.8 and 2.6 x10^3/µL), and their peripheral blast percentages were also low (10 and 58%, **Table 2**). Hypogranular APL patients of our cohort did not have severe hemorrhagic complications. The patients who relieved from early hemorrhagic complications have an excellent OS after ATRA era, as is our patients.

In our study, mean morphologic and cytogenetic remission by FISH analysis has been obtained at days 30.4 (15-45 days) and 51.7 (26-98 days), respectively. One may speculate that mean cytogenetic remission times were early because the FISH analysis is not sensitive to polymerase chain reaction (PCR) based methods to detect PML/RARA. We were not able to analyze PML/RARA translocation during treatment for all patients. Zhou et al.[14] reported that PML/RARA disappeared within 3 to 9 months after complete hematological response using PCR.

Although excellent remission rates, different from other AML types, might be attributable to ATRA, six patients in this study have experienced severe side effects such as PTC, pancarditis, and pulmonary infiltrates. Two patients suffered from DS while they were receiving AIDA protocol, but no DS was seen with AML BFM 2004 protocol. Otherwise, there was no difference in toxicity (e.g., heart) and efficacy between these protocols in this study. Pseudotumor cerebri incidence was reported to be 1.7 - 16% in patients on ATRA therapy.[30,31] In our study, PTC incidence was 17.6%, but clear definitions and incidence of this complication were not established. Botton et al.[31] recommended lower ATRA (25mg/m^2) doses to avoid from PTC. In contrast to that study, our patients were receiving low dose ATRA (25mg/m^2) courses when they developed PTC.

Conclusions. A high frequency (20.5%) of APL was noted among children with AML in this

single-center study. The overall mortality rate was 17.5%. Since the induction death rate was 12% and life-threatening bleeding was the primary

problem, awareness and urgent treatment are critical factors to reduce early losses.

References:

1. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann Intern Med. 1985; 103:620-5. https://doi.org/10.7326/0003-4819-103-4-620 PMid:3862359

2. Zhang L, Samad A, Pombo-de-Oliveira MS, Scelo G, Smith MT, Feusner J, Wiemels JL, Metayer C. Global characteristics of childhood acute promyelocytic leukemia. Blood Rev. 2015;29:101-25. https://doi.org/10.1016/j.blre.2014.09.013 PMid:25445717 PMCid:PMC4379131

3. Farah RA, Horkos JG, Bustros YD, Farhat HZ, Abla O. A Multicenter Experience from Lebanon in Childhood and Adolescent Acute Myeloid Leukemia: High rate of Early Death in Childhood Acute Promyelocytic Leukemia. Mediterr J Hematol Infect Dis. 2015;7(1):e2015012. https://doi.org/10.4084/mjhid.2015.012 PMid:25574371 PMCid:PMC4283923

4. Kömür M, Erbey F, Bayram I, Tanyeli A. Incidence and prognostic importance of molecular genetic defects in children with acute myeloblastic leukemia. Asian Pac J Cancer Prev. 2010;11:1393-5. PMid:21198299

5. Longo L, Pandolfi PP, Biondi A, Rambaldi A, Mencarelli A, Lo Coco F, Diverio D, Pegoraro L, Avanzi G, Tabilio A, Zangrilli D, Alcalay M, Donti E, Grignani F, Pelicci PG. Rearrangements and aberrant expression of the retinoic acid receptor alpha gene in acute promyelocytic leukemias. J Exp Med. 1990;172:1571-5. https://doi.org/10.1084/jem.172.6.1571 PMid:2175343

6. Lo-Coco F, Ammatuna E, Montesinos P, Sanz MA. Acute promyelocytic leukemia: recent advances in diagnosis and management. Semin Oncol. 2008;35:401-9. https://doi.org/10.1053/j.seminoncol.2008.04.010 PMid:18692690

7. Yan W, Zhang G. Molecular Characteristics and Clinical Significance of 12 Fusion Genes in Acute Promyelocytic Leukemia: A Systematic Review. Acta Haematol. 2016;136:1-15 https://doi.org/10.1159/000444514 PMid:27089249

8. Calleja EM, Warrell RP Jr. Differentiating agents in pediatric malignancies: all-trans-retinoic acid and arsenic in acute promyelocytic leukemia. Curr Oncol Rep. 2000; 2(6):519-23 https://doi.org/10.1007/s11912-000-0105-x

9. Huang ME, Ye YC, Chen SR, Chai JR, Lu JX, Zhoa L, Gu LJ, Wanq ZY. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988;72:567-72. PMid:3165295

10. Abla O, Ribeiro RC. How I treat children and adolescents with acute promyelocytic leukaemia. Br J Haematol. 2014;164:24-38. https://doi.org/10.1111/bjh.12584 PMid:24117210 PMCid:PMC5127390

11. Testi AM, Biondi A, Lo Coco F, Moleti ML, Giona F, Vignetti M, Menna G, Locatelli F, Pession A, Barisone E, De Rossi G, Diverio D, Micalizzi C, Aricò M, Basso G, Foa R, Mandelli F. GIMEMA-AIEOPAIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. Blood. 2005;106:447-53. https://doi.org/10.1182/blood-2004-05-1971 PMid:15677559

12. Creutzig U, Zimmermann M, Dworzak M, Urban C, Henze G, Kremens B, Lakomek M, Bourquin JP, Stary J, Reinhardt D. Favourable outcome of patients with childhood acute promyelocytic leukaemia after treatment with reduced cumulative anthracycline doses. Br J Haematol. 2010;149(3):399-409. https://doi.org/10.1111/j.1365-2141.2010.08107.x PMid:20230404

13. Mathews V, George B, Lakshmi KM, Viswabandya A, Bajel A, Balasubramanian P, Shaji RV, Srivastava VM, Chandy M. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. Blood. 2006;107:2627-32. https://doi.org/10.1182/blood-2005-08- 3532 PMid:16352810

14. Zhou J, Zhang Y, Li J, Li X, Hou J, Zhao Y, Liu X, Han X, Hu L, Wang S, Zhao Y, Zhang Y, Fan S, Lv C, Li L, Zhu L. Single-agent arsenic trioxide in the treatment of children with newly diagnosed acute promyelocytic leukemia. Blood. 2010;115:1697-702. https://doi.org/10.1182/blood-2009-07-230805 PMid:20029047

15. Kutny MA, Alonzo TA, Gerbing RB, Wang YC, Raimondi SC, Hirsch BA, Fu CH, Meshinchi S, Gamis AS, Feusner JH, Gregory JJJr. Arsenic Trioxide Consolidation Allows Anthracycline Dose Reduction for Pediatric Patients With Acute Promyelocytic Leukemia: Report From the Children's Oncology Group Phase III Historically Controlled Trial AAML0631. J Clin Oncol. 2017;35(26):3021-3029. https://doi.org/10.1200/JCO.2016.71.6183 PMid:28767288

16. Kelaidi C, Chevret S, De Botton S, Raffoux E, Guerci A, Thomas X, Pigneux A, Lamy T, Rigal-Huguet F, Meyer-Monard S, Chevallier P, Maloisel F, Deconinck E, Ferrant A, Fegueux N, Ifrah N, Sanz M, Dombret H, Fenaux P, Adès L. Improved outcome of acute promyelocytic leukemia with high WBC counts over the last 15 years: the European APL Group experience. J Clin Oncol. 2009;27:2668-76. https://doi.org/10.1200/JCO.2008.18.4119 PMid:19414681

17. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, Graf N, Klingebiel T, Kremens B, Lehrnbecher T, von Neuhoff C, Ritter J, Sander A, Schrauder A, von Stackelberg A, Starý J, Reinhardt D. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from Study AML-BFM 2004. Blood. 2013;122:37-43. https://doi.org/10.1182/blood-2013-02-484097 PMid:23704089

18. Cheson BD, Cassileth PA, Head DR, Schiffer CA, Bennett JM, Bloomfield CD, Brunning R, Gale RP, Grever MR, Keating MJ. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. J Clin Oncol. 1990;8:813-9. https://doi.org/10.1200/JCO.1990.8.5.813 PMid:2185339

19. Abla O, Ribeiro RC, Testi AM, Montesinos P, Creutzig U, Sung L, Di Giuseppe G, Stephens D, Feusner JH, Powell BL, Hasle H, Kaspers GJL, Dalla-Pozza L, Lassaletta A, Tallman MS, Locatelli F, Reinhardt D, Lo-Coco F, Hitzler J, Sanz MA. Predictors of thrombohemorrhagic early death in children and adolescents with t(15;17)-positive acute promyelocytic leukemia treated with ATRA and chemotherapy. Ann Hematol. 2017;96(9):1449-1456. https://doi.org/10.1007/s00277-017-3042-6 PMid:28597167

20. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The "retinoic acid syndrome" in acute promyelocytic leukemia. Ann Intern Med. 1992;117:292-6. https://doi.org/10.7326/0003-4819-117-4-292 PMid:1637024

21. Sanz MA, Lo Coco F, Martín G, Avvisati G, Rayón C, Barbui T, Díaz-Mediavilla J, Fioritoni G, González JD, Liso V, Esteve J, Ferrara F, Bolufer P, Bernasconi C, Gonzalez M, Rodeghiero F, Colomer D, Petti MC, Ribera JM, Mandelli F. 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(4):1247-53 PMid:10942364

22. Işık P, Çetin I, Tavil B, Azik F, Kara A, Yarali N, Tunc B. All-transretinoic acid (ATRA) treatment-related pancarditis and severe pulmonary edema in a child with acute promyelocytic leukemia. J Pediatr Hematol Oncol.2010;32(8):e346-8. https://doi.org/10.1097/MPH.0b013e3181e75731 PMid:20881874

23. Sainty D, Liso V, Cantù-Rajnoldi A, Head D, Mozziconacci MJ, Arnoulet C, Benattar L, Fenu S, Mancini M, Duchayne E, Mahon FX, Gutierrez N, Birg F, Biondi A, Grimwade D, Lafage-Pochitaloff M, Hagemeijer A, Flandrin G; Groupe Français d'Hématologie Cellulaire; Groupe Français de Cytogénétique Hématologique; UK Cancer Cytogenetics Group; BIOMED 1 European Community-Concerted Action "Molecular Cytogenetic Diagnosis in Haematological Malignancies". A new morphologic classification system for acute promyelocytic leukemia distinguishes cases with underlying PLZF/RARA gene rearrangements. Blood. 2000;96:1287-96. PMid:10942370

24. Gorczyca W. Acute promyelocytic leukemia: four distinct patterns by flow cytometry immunophenotyping. Pol J Pathol. 2012;63:8-17. PMid:22535601

25. Albano F, Mestice A, Pannunzio A, Lanza F, Martino B, Pastore D, Ferrara F, Carluccio P, Nobile F, Castoldi G, Liso V, Specchia G. The biological characteristics of CD34+ CD2+ adult acute promyelocytic leukemia and the CD34 CD2 hypergranular (M3) and microgranular (M3v) phenotypes. Haematologica. 2006;91:311-6. PMid:16531253

26. Cicconi L, Lo-Coco F. Current management of newly diagnosed acute

promyelocytic leukemia. Ann Oncol. 2016;27:1474-81. https://doi.org/10.1093/annonc/mdw171 PMid:27084953

27. Stein EM, Tallman MS. Acute promyelocytic leukemia in children and adolescents. Acta Haematol. 2014;132:307-12. https://doi.org/10.1159/000365117 PMid:25228556

28. Takahashi H, Watanabe T, Kinoshita A, Yuza Y, Moritake H, Terui K, Iwamoto S, Nakayama H, Shimada A, Kudo K, Taki T, Yabe M, Matsushita H, Yamashita Y, Koike K, Ogawa A, Kosaka Y, Tomizawa D, Taga T, Saito AM, Horibe K, Nakahata T, Miyachi H, Tawa A, Adachi S. High event-free survival rate with minimum-dose-anthracycline treatment in childhood acute promyelocytic leukaemia: a nationwide prospective study by the Japanese Paediatric Leukaemia/Lymphoma Study Group. Br J Haematol. 2016;174:437-43. https://doi.org/10.1111/bjh.14068 PMid:27029412

29. Mantha S, Goldman DA, Devlin SM, Lee JW, Zannino D, Collins M, Douer D, Iland HJ, Litzow MR, Stein EM, Appelbaum FR, Larson RA, Stone R, Powell BL, Geyer S, Laumann K, Rowe JM, Erba H, Coutre S, Othus M, Park JH, Wiernik PH, Tallman MS. Determinants of fatal bleeding during induction therapy for acute promyelocytic leukemia in the ATRA era. Blood. 2017;129:1763-1767. https://doi.org/10.1182/blood-2016-10-747170 PMid:28082441 PMCid:PMC5374291

30. Coombs CC, DeAngelis LM, Feusner JH, Rowe JM, Tallman MS. Pseudotumor Cerebri in Acute Promyelocytic Leukemia Patients on Intergroup Protocol 0129: Clinical Description and Recommendations for New Diagnostic Criteria. Clin Lymphoma Myeloma Leuk. 2016;16:146-51. https://doi.org/10.1016/j.clml.2015.11.018 PMid:26724834 PMCid:PMC5028896

31. de Botton S, Coiteux V, Chevret S, Rayon C, Vilmer E, Sanz M, de La Serna J, Philippe N, Baruchel A, Leverger G, Robert A, San Miguel J, Conde E, Sotto JJ, Bordessoule D, Fegueux N, Fey M, Parry A, Chomienne C, Degos L, Fenaux P. Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. J Clin Oncol. 2004;22:1404-12. https://doi.org/10.1200/JCO.2004.09.008 PMid:15084614