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ACUTE PROMYELOCYTIC LEUKEMIA (APL): DIAGNOSIS AND TREATMENT

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ABSTRACT: Background:Acute Promyelocytic Leukemia (APL) is a subgroup of Acute Myeloid Leukemia(AML) with a different certain clinical period, biology and treatment. APL was the deadly leukemia but today it is most curable leukemia so that it could be treated with low cytotoxicity drugs such as All -Trans- Retinoic Acid (ATRA, tretinoin), and the best consolidation treatment in recurrence cases is Arsenic Trioxide (ATO,Trisenox). The purpose of this article is to introduce the APL, features and provides a rationale for the plan of risk-adapted protocols for further improving treatment outcome for this type of leukemia and reduce cytotoxicity of treatment protocols. **Method**: Search was performed on PubMed, MEDLINE, Science direct and Google scholar by using of keywords such as APL, treatment, M3 variant, various translocations. **Result**: we found 200 articles which we selected58 articles which have most relation with our subject.11articles about introduction, 9 articles about epidemiology and 38 articles about treatment.Articles werestudied and finally extracted their information. **Conclusion**: There are a series of tests for the diagnosis of APL, including Immunophenotyping, Histochemical methods such as Myeloperoxidase(MPO), Sudan black B is positive and periodic acid Schiff (PAS) is negative and Nonspecific esterase <5% is weak positive and another diagnostic method is SpSp expression in AML-M3, M4. APL treatment was done with target therapy that was a new vision for leukemia treatment in order to use of drugs that have less toxicity and have the best response to treatment. It is associated with different translocation that is always involving retinoic acid receptor-α (RAR-α) gene with a variable partner gene (X-RARα or RARAα-X) that PML gene is the most partner gene. The partner gene has an impact on the response to ATRA,So that, 95% of patients were responsive to treatment with ATRA. The initial WBC and platelet count make associated with relapse, and determined the protocol cure and use or non-use of chemotherapy.

KEYWORDS:APL, ATRA, ATO, Complete Remission (CR)

INTRODUCTION:

Acute Myeloid Leukemia(AML), is one of the hematological malignancies. APLis a subgroup of Acute Myeloid Leukemia(AML) with a different certain clinical period and a biology and treatment .(1)APL was first described as an entity in the late 1950s in Norway and France as a hyper acute fatal sickness linked with a hemorrhagic syndrome.(2) In 1959, Jean Bernard, et al. defined the relation of APL with an intense hemorrhagic diathesis (congenital, often hereditary, capacity of the body to a malady) that lead to disseminated intravascular coagulation (DIC) and hyper fibrinolysis.(3)

In 1973, there were publications of complete remission (CR) with treatment of APL via daunorubicin(DNR).(4) In 1974, Leo Sachs pioneered research on leukemic cell differentiation in vivo.(5) Zhen-Yi Wang, shared data on the influence of ATRA in APL patients in 1985.(6) There were multiple reports in 1990 that related a translocation between chromosomes 15 and 17 to the pathology of APL.(7) In the primary to middle 1990s, ATO was added to the treatment of APL. A potentially deadly complication of ATRA treatment, named RAS, was described. finally

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APL has converted from a extremely fatal disease to an extremely treatable disease.(8, 9)In a study conducted by Fenaux, P, et al noted that in the past, intensive chemotherapy, usually combining an anthracycline and ARA-C(cytosine arabinoside), was the only effective treatment for APL. the advent of ATRA, and recently of As2O3,has highly improved the therapeutic procedure of APL.(10)Incidence rate in APL is About 10% of AMLthat is the most common type of AML after M2.(9, 11)APL is identical in both sexes, it can occur at any age that the mean age of M3 patients was 25-29 years.(11)

EPIDEMIOLOGY:

Despite significant improvements in the prognosis and treatment of APL, understanding of the epidemiology of APLremnants restricted.(12) The annual incidence of APL in Italy was approximately 0.6 cases per 1 million people.(1)In 1996s the ratio of APL among the 80 AML patients of Latino origin was higher (37.5%)than the 62 non-Latinosin (6.5%).(1, 13)APL shows a signallynumerous frequency between countries in South America including Brazil that involved in Campinas 21.1% and Teresina7.8%.(14, 15)In the study with Matthew J. Matasara and et.al cannot confirm the conclusion of previous investigators that frequency of APL has higher in Hispanics than non-Hispanics, although they did find that there is a different age distribution in the incidence rates among different races and ethnic groups.(12)In Mazandaran of Iran province, 1,146 cases of leukemia and lymphoma have been realized since 2001-2008, Myeloid leukemia: In the average have about 1.1 per 100,000 incidence rate annually. The highest incidence rate was seen in the age group of 70 years and above and the lowest incidence rate was seen in the age group of 0 to 9 years. Incidence rate in the male was calculated 1 per 100,000 and in the female 1.1 per 100,000. Male to female ratio is 0.9. The highest incidence rate in Iran was seen in Ghaemshahr and the lowest incidence rate was seen in Mahmoodabad.(16)In Northwest Iranin in years of 1996-2003We diagnosed 483 patients with AML, with an age range of 31-60. 70% were from East Azarbaijan, 20%West Azarbaijan, 5.2%Kordestan, 4%Ardabil and 0.8%Zanjan thatthe prevalent M3subtype was 19.4%.(17)AML diagnosed in Gharbiah(Northern Egypt) in 1999–2005 is 266 cases that number of APL is 30 cases (11%) that in male is16 and women is 14 cases therefor incidence rate of APLis equal in men and women.(18)AML is scarce among the Lebanese population.They identified 24 children with AML From 2002-2010 that 25% of patients had APL.(19)In Saudi Arabia with Flow cytometric analysis was detected that incidence rate M3 is 23%. (20)Of all the 3897 acute leukemias from 1997 to 2006 in the Swedish Adult Acute Leukemia Registry, were 3205 (82%) patients with non-APL, that APL, involved 2.7% of allacute leukemias and 3.2% of all AMLs and the mean age was 54 years (21)and in the other study median age was 36.(8)

CLINICALPRESENTATION:

Like any acute leukemia, notable decrease in their prior level of activity, Unusual bleeding, bruising, blondness, fatigue, breathlessness, repeated and resistant infections, chest distress ,weight loss (20 kg), and five episodes of tonsillitis.(9, 22)50% of M3 cases reported with fever and bleeding manifestation was most frequent.(11) ≥50% APLs have coagulation disorders including a high risk of life-threatening intracerebral hemorrhages, bleeding into the skin, the mucous membranes, the gastrointestinal tract, and the lungs referred. The bleeding trend depends on the intensity of thrombocytopenia (decrease of platelets in blood).(9)

DIAGNOSIS:

There are a series of tests for the diagnosis of APL, including: Immunophenotyping recognized with marked antibody anti specific marker, so that Immunophenotypic positive marker isCD13, 33,117,11c, 9 and negative marker is HLA-DR ,CD2,14,41,61,11b,10,7 in the APL. Histochemical is other diagnostic methods such as Myeloperoxidase(MPO), Sudan black B is positive and periodic acid Schiff (PAS) is negative and Nonspecific esterase <5% is weak positive.(22, 23)Two MPO alleles differ that areclledSp and N.Another diagnostic method is SpSp (homozygote genotype) expression in AML-M3, M4. The standard cells is 61%,whiles these subtypes are 79% to 82%. The SpSp genotype is further shown to be related with superior levels of MPO mRNA than the SpN(heterozygote genotype) or NN genotypes in initial AML cells. That the over-expressing SpSp MPO genotype is cause of superior MPO levels that are related with an increased danger for this subtypes.(24)

Specific APL analyses rapidly should be confirmed by RT-PCR test (reverse transcription-polymerase chain reaction is the most sensitive technique for mRNA detection and quantification), FISH (fluorescence in situ hybridization) for the specific translocation and immunofluorescence for expression of PML (progressive multifocal leukoencephalopathy) are considered as equivalent for this aim. However, the PML/RARA isoform estimate by means RT-PCR andused for the later monitoring of Minimal Residual Disease (MRD). Monitoring can'tdo by applying each other technique because sensitivity of RT-PCR is more than FISH.Autofluorescence(the light emitted naturally by an unstained, illuminated cell) in APL is an identified phenomenon in flowcytometry, little consideration has been paid to its potential diagnostic advantage.This autofluorescence can be distinguished from the non-specific Fc binding of monocytic leukemic cells by observation of equal binding of all control antibodies and an identical fluorescence pattern in both unstained cells and controls,therefore, it can utilization as a helpful auxiliary diagnostic marker in APL.(8, 28) An anti-PML (PG-M3) antibody is useful for immunofluorescent staining of microparticulate PML protein in the classical APL that is another rapid and efficient method.(29)

Table 1- Morphologic subtypes

	Hypergranular (Classic M3)	**Microgranular (M3V)**	**Hyperbasophilic**	**M3r**
Nucleus	Folded, lobulated; granules obscure borders	Irregular, folded, bibbed large nucleoli	High nucleocytoplasmic ratio and irregular lobulated	regular round or ovalcondensed chromatin pattern; Pelger-like cells
Cytoplasm	distinguished azurophilic granules	fine granules; dust-like, Pelger-like cells, alike to monocytic subtypes (AML4,5),but ANAE is negative.	Granules diffused, powerfully basophilic cytoplasm with budding , alike to micromegakaryocyte	Granularity between M3 and M2
Auer rods	Frequent;faggot cells	Rare	Not seen	Rare
Ref	(25)	(26)	(27)	(25)
This table is provide differentiation of the APL variants from aspiration sample.				

Table2-Karyotype/cytogenetic

Subtype	Frequency (%)	Gene	Function "X," RARα partner gene	ATRA response	Ref
M3/M3vt(15;17) (q22;q21) Favourable	95	PML-RARA Bcr1 Bcr2 Bcr3	Transcriptional factor, Zinc finger	+	(30)
t(11;17)(q23;q21)	<5	PLZF-RARA	Developmental/differentiation control, zinc finger (ZBTB16)	-	(22, 31, 32)
t(11;17)(q13;q21)	<1	NuMA-RARA	Structural role in mitosis, apoptosis, interphase nuclear matrix	±	(33)
t(5;17)(q32; q12)	<1	NPM-RARA	Ribonucleoprotein maturation and transport	±	(34)
t(17;17) (q11,q21)	<1	STAT5b-RARα	Signal transduction, transcriptional factor	-	(35)
isochromosome of the long arm of chromosome 17 i(17)(q10)	<1	-----	-----	+	(36)
t(X;17)(p11.4;q21)	<1	BCOR-RARA	BCL6 corepressor	+	(37)
t(4;17)(q12;q21)	<1	FIP1L1-RARA	Function is not clear	+	(38)
t(2;17)(q32;q21)	<1	OBFC2A/RARA	A partial of complex SOSS (sensor of single-stranded DNA)	+	(39)
t(17;17) (q11,q24)	<1	PRKAR1A-RARA	regulatory subunit type I-α of cyclic adenosine monophosphate–dependent protein kinase	+	(40)
PML distrib is Abnormal in t(15;17).(41)					

TREATMENT PATIENTS:

Supportive measures are including : Maintenance the platelet (Plt) count ≥30-50×109/L with Plt transfusions if necessary, Maintain hemoglobin levels > 8 g/dL with packed cell transfusions if necessary, Maintain the plasma fibrinogen level ≥1-1.5 g/L,Management of coagulopathy with Fresh frozen plasma and cryoprecipitate transfusions if necessary,use of Anticoagulants for Preventation of DIC, Dexamethasone o Methylprednisolone or prednisone (0.5 mg/kg/d×15 orally) for Retinoic acid syndrome (RAS) prophylaxis, Intrathecal injection of methotrexate, Ara-C(cytosine arabinoside), Prednisolone before the start of the third consolidation for CNS prophylaxis, antifungal and antimicrobial prophylaxis until Reach Neutrophils >1000/L, Treatment with leukopheresis, low molecular heparin or inhibitors of fibrinolysis was not usually suggested.(32, 42, 43)

Prognostic and Risk factors for relapse and survival including age, sex, initial WBC count, RAS, new case v.s relapsed case, and MRD status.Hyperleukocytosis, senility (44), Increased LDH(lactate dehydrogenase), Increased BMI(body mass index)(45, 46) are Bad Prognosis. According toPethemaprotocol patients based on Initial WBCand Platelet counts(PLT) divided three group Low risk with PLT > 40 and WBC <10, Intermediate risk PLT < 40 and WBC <10, High risk WBC ≥ 10 .(47, 48)

TREATMENT COURSES:

The GIMEMA and PETHEMA protocols was based on a common CHT backbone, including identical induction (ATRA + IDA(idarubicin)or anthracyclineactually No do comparison between the anthracycline, daunorubicin(DNR) and idarubicin.) that About 90% of APLs go into remission and if added Ara-C can be improved prognosis of high-risks, but the role of cytarabine in the treatment of APL is disputable. and maintenance therapies (ATRA + mercaptopurine, methotrexate), as well as the similar dose protocol of intercalating drugs (IDA and MTZmitoxantrone) for consolidation. The only difference was the omission of nonintercalating drugs from consolidation in the PETHEMA schedule.(49-51)

In the GIMEMA protocol showed that CR: 94.3% /Induction death: 5.5% / Resistance: 0.2% /RAS: 13% /6 years-OS(overall survival):78.1% /6-year DFS(disease free survival):69.5% and in the high-risk is 49.6% / 6-year CIR(cumulative incidence of relapse):27.7%.(52) And for PETHEMA protocol is about CR: 9o% /Induction death: 5.5% / Resistance: 0.2% /RAS: 13% /6 years-OS:78.1% /6-year DFS:69.5% and in the high-risk is 49.6% / 6-year CIR:27.7%.

Induction therapy a standard panel is ATRA+chemotherapy with CR rates about 90%. According to studies and compartion between ATRA + chemotherapy and ATRA or chemotherapy alone showed better outcomes in the using of ATRA + chemotherapy that it`s results for 5-year is OS: 87 ± 9%, RFS(relapse-free survival): 83 ±7%, EFS: 74 ±3, DFS: 82 ±14%,and in High-Risk Patients is OS: 83±12%,EFS(event-free survival): 69%, DFS: 68 ±24%.(32, 42, 49, 51-53)

All -Trans- Retinoic Acid (ATRA, tretinoin) :A substance of vitamin A that improves differentiation of promyelocytes into neutrophil and reduces the number of leukemic blast cells in the marrow and reduces the side effects of chemotherapy. At least 80% of patients achieve short-term remission with lonely ATRA. For long-term remission, ATRA+chemotherapywill be used with or after induction therapy. ATRA without chemotherapy couldn't induce a long-term remission.(23)ATRA is recommended ceaselessly until CR is obtained, at maximum up to a period of 60 days or treatment should be continued until achievement of CR.(42)

ATRA related toxicity: RAS, intense headache, Pseudotumorcerebri, Pleural effusion , labored breathing , intense bone ache. ATRA is known to be teratogenic.(32)ATRA syndrome : APL

differentiation syndrome (over weight, high temperature, polyserositis and difficulty breathing. likely with radiographic markers of pulmonary effusion) was treated by intravenous dexamethasone 10 mg twice daily for a least of 3 days and ATRA ceased temporarily until the signs improved.(32, 54) Patients whose RAS improved to adult respiratory distress syndrome or pulmonary hemorrhage, promptly used aided ventilation with oxygen and Novoseven.(48) Extramedullary disease (EMD) in APL can happen at relapse, however it is a so scarce clinical incident at diagnosis.(50)Incidence rate of RAS is higher in females than males.(55)

About 70-80% of APLs go into remission after being treated with ATRA and an anthracycline, such as IDA. Although, partly problems can happen, such as: haemorrhage during the treatment's primary phases or resistance to treatment or relapse. Patients in remission must get long-term follow-up to determine whether they are cured or need further therapy. The perfect duration of maintenance therapy is also being searched. Currently, it consists of 2 years of ATRA + mercaptopurine, methotrexate.(9)

Early death firstly because of hemorrhage(41% of the EDs) before and during induction therapy currently remains the main cause for treatment failure in APL. 35% of EDs never received ATRA treatment. The ED rates uprose with

increasing age and clearly with poor performance situation and related with high WBC, lactate dehydrogenase(LDH), creatinine, C-reactive protein(CRP) and low platelet.(14, 21, 44)

Arsenic Trioxide (ATO,Trisenox) :ATO is effective for treatment of relapsed or refractory APLs resistant to ATRA and as firstly treatment for APL or they've shown persistent MRD(minimal level of remaining APL cells can't be detected by standard tests), after post-remission therapy Patients who don't have a donor, or can't have an allogeneic stem cell transplant for other reasons, may be candidates for an autologous stem cell transplantation.(9, 48, 56), so we suggest that ATO is superior to ATRA for new cases and can induce a durable remission and good DFS, APLs treated with ATO, the most important limitation was RAS, which is occasionallyfatal.(48)The single-agent ATO-based regimen could be recommended in the good-risk group, patients where standard chemotherapy can't be administered due to poor efficiencysituation, comorbidities, and in the senile, pregnancy. That ATO can be an effective curative alternative choice andthat`s results for 5-year is OS: 74.2 ± 5.2%, RFS:69 ± 5.5%, EFS:80 ± 5.2% and in High-Risk Patients is OS:63±7%, EFS: 60 ± 7% .(57)

Consolidation therapy done minimum 2 or 3 cycles with intensivebased chemotherapy(DNR, IDA, AraC), molecular remission Obtained in 90–99% of patients, therefor this policy has as the standard, furthermore GIMEMA and PETHEMA indicate a synergistic effect and improve of ATRA +chemotherapy. Cases who show residuary PML/RARα transcripts at the end of consolidation course should be received further intensification, whereas those who have negative PCR test should be received maintenance. In High-Risk Patients is like three course other groups, with the exception that cytarabine added.(32, 42, 49, 52)

Chemotherapy: The chemotherapy protocol depended on the initialWBCand Blast count in the peripheral blood.**(42)**If WBC count and Blast count respectively are < 3.0×109/L and < 1.0×109/L, simultaneous chemotherapy was withheld with CR rate 92%, if they are 3.0-10.0×109/L, > 1.0×109/L, are used idarubicin (IDA) 12 mg/m²/d ×2 +cytarabine (AraC) 100 mg/m²/d ×5 with CR rate 91%,and if WBC count is ≥ 10.0×109/L, are used IDA 12 mg/m²/d ×3 +AraC 100 mg/m²/d ×75 with CR rate 87%.(42)

Maintenance therapy has been firmly established for first-remission APL only, where a combination of long-term chemotherapy (mercaptopurine and methotrexate) and ATRA is warranted.(56)In the comparing done between ATRA v.sTamibarotene(synthetic retinoid) for 14 days every 3 months for 2 years that no statistical difference between ATRA and tamibarotene, although there was a suggestion of improved efficacy of tamibarotene in high-risk patients in an exploratory analysis. So thatin the using of tamiboratene 4 years-RFS is 91% and high risk group is 87% versus in the using of ATRA is 84% vs high risk group is 58%.(32, 42)

MRDafter the consolidation phase and 12 months after CR, 48 patients evaluated with RT–PCR studies on blood samplewith Sensitivity of RT–PCR was 10^{-3}, searching for mRNA of PML-RARA isoforms.So that ifRT-PCR result is negative 5-year OS 92.3 ± 5.3% 5-year RFS 91.8 ± 4.1% and if it is not negative OS o RFS is respectively 65.2 ± 13.0%, 59.1 ± 12.2%.(8)

CR WAS DEFINED AS THE PRESENCE OF ALL OF THE FOLLOWING :

< 5% of blasts in the bone marrow, marrow cellularity >20% with trilineage maturation, and marrow blast < 5% , with no Auer rod visible, no leukemic blasts in the peripheral blood or extramedullary sites, and recovery of peripheral-blood counts, < 100 copies/μgRNAwere detected with real-time quantitative reverse transcription polymerase chain reaction assay defined as molecular remission, ≥10 g/dL Hemoglobin without transfusing,≥1.5 × 109/L Neutrophils, ≥100 × 109/L platelets.(8, 33)

RELAPSE TREATMENT :

ATRA should not be used as alone factor therapy due to a notable probability of acquired secondary resistance and ATO should only be used in PML– RARA positive.Agothe advent of ATO, in relapsed APL, rescue therapy included

of a reinduction with ATRA + chemotherapy (anthracycline or mitoxantrone and intermediate or high doses of cytarabine, with or without etoposide), usually followed by consolidation with additional chemotherapy and HSCT. That gives in high rates of second CR (80-90%).(54)with As2O3 0.15 mg/kg intravenous (IV) infusion until CR that molecular remission is nearly 80% of patients with relapse and 1 - 3 years OS is 50 -70%. After CR with 2-4 consolidation therapy in the same protocol as remission induction.(58)Hematopoietic stem cell transplantation(HSCs) with use of autologous or allogeneic transplantation as consolidation should be conducted via MRD analysis.The recognition patients at higher risk of extra relapse with persistent positive PCR who must be candidate for allogeneic HSCT.(21, 54)

MANAGEMENT OF PARTICULAR CONDITIONS:

High-risk patients older than 60 years and patients with severe comorbidities treated withless intensive regimens and they are volunteers for substitute front-line procedure using ATRA, ATO.(49)In the high-risks, combination of ATO with ATRA and chemotherapy can be reduced the risk of relapse.(57)

CONCLUSION:

There are a series of tests for the diagnosis of APL, including Immunophenotyping, Histochemical methods such as Myeloperoxidase(MPO), Sudan black B is positive and periodic acid Schiff (PAS) is negative and Nonspecific esterase <5% is weak positive and another diagnostic method is SpSp

expression in AML-M3, M4. APL treatment was did with target therapy that was a new vision for leukemia treatment in order to use of drugs that have less toxicity and have the best response to treatment. It is associated with different translocation that is always involving retinoic acid receptor-α (RAR-α) gene with a variable

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REFERENCES:

1. Douer D. The epidemiology of acute promyelocytic leukaemia. Best Practice & Research Clinical Haematology. 2003;16(3):357-67.
2. Nadir Y, Katz T, Sarig G, Hoffman R, Oliven A, Rowe JM, et al. Hemostatic balance on the surface of leukemic cells: the role of tissue factor and urokinase plasminogen activator receptor. haematologica. 2005;90(11):1549-56.
3. Bernard J, Mathe G, Boulay J, Ceoard B, Chome J. Acute promyelocytic leukemia: a study made on 20 cases. Schweizerische medizinische Wochenschrift. 1959;89:604.
4. Bernard J, Weil M, Boiron M, Jacquillat C, Flandrin G, Gemon M-F. Acute promyelocytic leukemia: results of treatment by daunorubicin. Blood. 1973;41(4):489-96.
5. Lotem J, Sachs L. Different blocks in the differentiation of myeloid leukemic cells. Proceedings of the National Academy of Sciences. 1974;71(9):3507-11.

6. Wang Z-Y, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008;111(5):2505-15.
7. Allford S, Grimwade D, Langabeer S, Duprez E, Saurin A, Chatters S, et al. Identification of the t (15; 17) in AML FAB types other than M3: evaluation of the role of molecular screening for the PML/RARα rearrangement in newly diagnosed AML. British journal of haematology. 1999;105(1):198-207.
8. 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. Leukemia research. 2007;31(6):765-71.
9. Myelomonocytic J. Cancer Association of South Africa (CANSA).
10. Fenaux P, Chomienne C, Degos L, editors. All-trans retinoic acid and chemotherapy in the treatment of acute promyelocytic leukemia. Seminars in hematology; 2001: Elsevier.
11. Hassan K, Qurshi M, Shafi S, Ikram N. Acute myeloid leukemia-FAB classification and its correlation with clinico-haematological features. JOURNAL-PAKISTAN MEDICAL ASSOCIATION. 1993;43:200-.
12. Matasar MJ, Ritchie EK, Consedine N, Magai C, Neugut AI. Incidence rates of acute promyelocytic leukemia among Hispanics, blacks, Asians, and non-Hispanic whites in the United States. European journal of cancer prevention. 2006;15(4):367-70.
13. Douer D, Preston-Martin S, Chang E, Nichols P, Watkins K, Levine A. High frequency of acute promyelocytic leukemia among Latinos with. Blood. 1996;87(1):308-13.
14. 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(5):853-4.
15. Rego M, Pinheiro G, Metze K, Lorand-Metze I. Acute leukemias in Piauí: comparison with features observed in other regions of Brazil. Brazilian journal of medical and biological research. 2003;36(3):331-7.
16. Tahmasby B, Marnani AB, Maleki M, Barouni M, Mousavi SH, Naseriyan B, et al. Blood malignancies in Mazandaran province of Iran. Asian Pac J Cancer Prev. 2013;14:1053-6.
17. Ziaei JE. High frequency of acute promyelocytic leukemia in northwest Iran. Asian Pacific Journal of Cancer Prevention. 2004;5(2):188-9.
18. Herzog C, Dey S, Hablas A, Khaled H, Seifeldin I, Ramadan M, et al. Geographic distribution of hematopoietic cancers in the Nile delta of Egypt. Annals of oncology. 2012;23(10):2748-55.
19. 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. Mediterranean journal of hematology and infectious diseases. 2015;7(1).
20. Rayyan G, Shubair M, Asiri M. Flow Cytometric Analysis of Acute Leukemia Cases in Aseer Area of the Kingdom of Saudi Arabia. 2012.
21. Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Möllgård 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(7):1128-34.
22. Rohr SS, Pelloso LAF, Borgo A, De Nadai LC, Yamamoto M, Rego EM, et al. Acute promyelocytic leukemia associated with the PLZF-RARA fusion gene: two additional cases with clinical and laboratorial peculiar presentations. Medical Oncology. 2012;29(4):2345-7.
23. Dervesteanu M, ONISAI M, BUMBEA H, RADESI S, CIUFU C, NICOLESCU A, et al. Acute promyelocytic leukemia microgranular variant–A clinical and therapeutical approach. Mædica A Journal of Clinical Medicine. 2007;2(4):328.

24. Reynolds WF, Chang E, Douer D, Ball ED, Kanda V. An allelic association implicates myeloperoxidase in the etiology of acute promyelocytic leukemia. Blood. 1997;90(7):2730-7.
25. Sainty D, Liso V, Cantù-Rajnoldi A, Head D, Mozziconacci M-J, Arnoulet C, et al. A new morphologic classification system for acute promyelocytic leukemia distinguishes cases with underlyingPLZF/RARA gene rearrangements. Blood. 2000;96(4):1287-96.
26. Golomb H, Rowley J, Vardiman J, Testa J, Butler A. " Microgranular" acute promyelocytic leukemia: a distinct clinical. Blood. 1980;55(2):253.
27. McKenna RW, Parkin J, Bloomfield CD, Dorothy Sundberg R, Brunning RD. Acute promyelocytic leukaemia: a study of 39 cases with identification of a hyperbasophilic microgranular variant. British journal of haematology. 1982;50(2):201-14.
28. Hayden PJ, O'Connell NM, O'Brien DA, O'Rourke P, Lawlor E, Browne PV. The value of autofluorescence as a diagnostic feature of acute promyelocytic leukemia. haematologica. 2006;91(3):417-8.
29. Gomis F, Sanz J, Sempere A, Plumé G, Senent ML, Pérez ML, et al. Immunofluorescent analysis with the anti-PML monoclonal antibody PG-M3 for rapid and accurate genetic diagnosis of acute promyelocytic leukemia. Annals of hematology. 2004;83(11):687-90.
30. Okada M, Miyazaki T, Kumota K, Kaneko Y, Sakurai M. 15/17 translocation in acute promyelocytic leukaemia. The Lancet. 1977;309(8018):961.
31. Chen Z, Brand NJ, Chen A, Chen S-J, Tong J-H, Wang Z-Y, et al. Fusion between a novel Krüppel-like zinc finger gene and the retinoic acid receptor-alpha locus due to a variant t (11; 17) translocation associated with acute promyelocytic leukaemia. The EMBO journal. 1993;12(3):1161.
32. Dorantes-Acosta E, Medina-Sanson A, Jaimes-García Y, López-Martínez B. Clinical features and treatment outcomes of pediatric acute promyelocytic leukemia in a Mexican pediatric hospital. Revista de investigación clínica; organo del Hospital de Enfermedades de la Nutrición. 2013;65(5):392.
33. Wells RA, Catzavelos C, Kamel-Reid S. Fusion of retinoic acid receptor α to NuMA, the nuclear mitotic apparatus protein, by a variant translocation in acute promyelocytic leukaemia. Nature genetics. 1997;17(1):109-13.
34. Redner RL, Rush E, Faas S, Rudert W, Corey S. The t (5; 17) variant of acute promyelocytic leukemia expresses a nucleophosmin-retinoic acid receptor fusion. Blood. 1996;87(3):882-6.
35. Dong S, Tweardy DJ. Interactions of STAT5b-RARα, a novel acute promyelocytic leukemia fusion protein, with retinoic acid receptor and STAT3 signaling pathways. Blood. 2002;99(8):2637-46.
36. Lee GY, Christina S, Tien SL, Ghafar ABA, Hwang W, Lim LC, et al. Acute promyelocytic leukemia with PML-RARA fusion on i (17q) and therapy-related acute myeloid leukemia. Cancer genetics and cytogenetics. 2005;159(2):129-36.
37. Ichikawa S, Ishikawa I, Takahashi T, Fujiwara T, Harigae H. Successful treatment of acute promyelocytic leukemia with at (X; 17)(p11. 4; q21) and BCOR-RARA fusion gene. Cancer genetics. 2015;208(4):162-3.
38. Kondo T, Mori A, Darmanin S, Hashino S, Tanaka J, Asaka M. The seventh pathogenic fusion gene FIP1L1-RARA was isolated from at (4; 17)-positive acute promyelocytic leukemia. Haematologica. 2008;93(9):1414-6.
39. Won D, Shin SY, Park C-J, Jang S, Chi H-S, Lee K-H, et al. OBFC2A/RARA: a novel fusion gene in variant acute promyelocytic leukemia. Blood. 2013;121(8):1432-5.
40. Catalano A, Dawson MA, Somana K, Opat S, Schwarer A, Campbell LJ, et al. The PRKAR1A gene is fused to RARA in a new variant acute promyelocytic leukemia. Blood. 2007;110(12):4073-6.
41. Fenu S, Mancini M, Duchayne E, Mahon F-X, Gutierrez N, Birg F, et al.

A new morphologic classification system for acute promyelocytic leukemia distinguishes cases with underlying PLZF/RARA gene rearrangements. Blood. 2000;96(4).

42. Shinagawa K, Yanada M, Sakura T, Ueda Y, Sawa M, Miyatake J, et al. Tamibarotene as maintenance therapy for acute promyelocytic leukemia: Results from a randomized controlled Trial. Journal of Clinical Oncology. 2014;32(33):3729-35.
43. Avvisati G, Petti MC, Lo-Coco F, Vegna ML, Amadori S, Baccarani M, et al. Induction therapy with idarubicin alone significantly influences event-free survival duration in patients with newly diagnosed hypergranular acute promyelocytic leukemia: final results of the GIMEMA randomized study LAP 0389 with 7 years of minimal follow-up. Blood. 2002;100(9):3141-6.
44. 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(5):1248-54.
45. Estey E, Thall P, Kantarjian H, Pierce S, Kornblau S, Keating M. Association between increased body mass index and a diagnosis of acute promyelocytic leukemia in patients with acute myeloid leukemia. Leukemia. 1997;11(10):1661-4.
46. Breccia M, Mazzarella L, Bagnardi V, Disalvatore D, Loglisci G, Cimino G, et al. Increased BMI correlates with higher risk of disease relapse and differentiation syndrome in patients with acute promyelocytic leukemia treated with the AIDA protocols. Blood. 2012;119(1):49-54.
47. Sanz MA, Coco FL, Martın G, Avvisati G, Rayón 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(4):1247-53.
48. Ghavamzadeh A, Alimoghaddam K, Ghaffari S, Rostami S, Jahani M, Hosseini R, et al. Treatment of acute promyelocytic leukemia with arsenic trioxide without ATRA and/or chemotherapy. Annals of Oncology. 2006;17(1):131-4.
49. Sanz MA, Montesinos P, Rayón C, Holowiecka A, De La Serna J, Milone G, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood. 2010;115(25):5137-46.
50. Mueller B, Buerger A, Solenthaler M, Garamvoelgyi E, Oppliger-Leibundgut E, Fey M, et al. Pleural tumors as sole primary manifestation of acute promyelocytic leukemia. Annals of oncology. 2006;17(4):722-3.
51. Lengfelder E, Haferlach C, Saussele S, Haferlach T, Schultheis B, Schnittger S, et al. High dose ara-C in the treatment of newly diagnosed acute promyelocytic leukemia: long-term results of the German AMLCG. Leukemia. 2009;23(12):2248-58.
52. Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood. 2010;116(17):3171-9.
53. Ortega JJ, Madero L, Martín G, Verdeguer A, García P, Parody R, et al. Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. Journal of Clinical Oncology. 2005;23(30):7632-40.
54. Milligan D, Grimwade D, Cullis J, Bond L, Swirsky D, Craddock C, et al. Guidelines on the management of acute myeloid leukaemia in adults. British journal of haematology. 2006;135(4):450-74.

55. Elemam O, Abdelmoety D. Acute promyelocytic leukemia, study of predictive factors for Differentiation Syndrome, single center experience. Journal of the Egyptian National Cancer Institute. 2013;25(1):13-9.
56. Fey M, Dreyling M. Acute myeloblastic leukaemias and myelodysplastic syndromes in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010;21(suppl 5):v158-v61.
57. Mathews V, George B, Chendamarai E, Lakshmi KM, Desire S, Balasubramanian P, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: long-term follow-up data. Journal of Clinical Oncology. 2010;28(24):3866-71.
58. Alimoghaddam K, Ghavamzadeh A, Jahani M, Mousavi A, Iravani M, Rostami S, et al. Treatment of relapsed acute promyelocytic leukemia by arsenic trioxide in Iran. Archives of Iranian medicine. 2011;14(3):167.

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