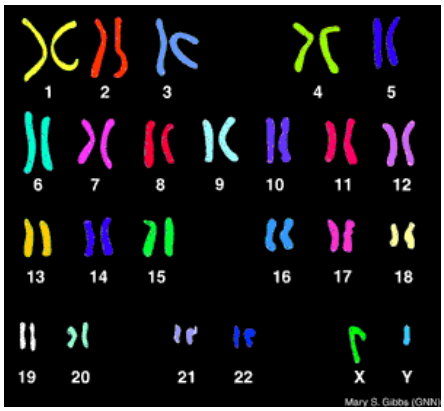
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Adult Acute Promyelocytic Leukaemia (APL)

Introduction

Acute promyelocytic leukaemia (APL) is a form of cancer that affects the stem cells which produce myeloid blood cells in the bone marrow.

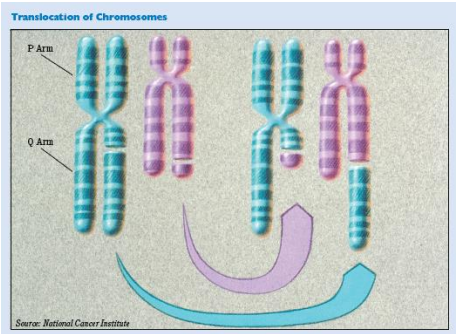


[Picture Credit: Karyotype]

Acute Promyelocytic Leukaemia

Acute promyelocytic leukaemia (APML, APL) is a subtype of acute myelogenous leukaemia (AML), a cancer of the white blood cells. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. The disease is characterised by a chromosomal translocation involving the retinoic acid receptor alpha (*RARα* or *RARA*) gene and is distinguished from other forms of AML by its responsiveness to all-trans retinoic acid (ATRA; also known as tretinoin) therapy. (Genetic Home Reference).

[Picture Credit: Chromosomal Translocation]



APL represents a medical emergency with a high rate of early mortality, often due to haemorrhage from a characteristic coagulopathy (abnormal blood coagulation). It is critical to start treatment with a differentiation agent (e.g., all-trans retinoic acid) without delay as soon as the diagnosis is suspected based upon cytologic criteria, and even before definitive cytogenetic or molecular confirmation of the diagnosis has been made. (Avvisati, 2011).

Sun, J., Zhu, J, Zhou, Zhu, L., Yang, X., Xie, M., Li, L., Huang, X., Zhu, M., Zheng, Y., Xie, W. & Ye, X. 2019.

PURPOSE: To perform a retrospective analysis of the prognostic relevance of clinicopathologic parameters in a well-documented cohort of patients treated with all-trans-retinoic acid (ATRA)-based induction regimens in order to discover which indicators can predict a high risk of early death (ED) and patient survival.

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PATIENTS AND METHODS: We analyzed data of 288 newly diagnosed adult acute promyelocytic leukemia patients in Hangzhou, China. The median follow-up time was 32 months (range, 6-78 months).
RESULTS: The 3-year disease-free and overall survival rates were 90.83% and 91.69%, respectively. In the multivariable analysis, older age (≥ 60 years) was the only independent risk factor for ED (hazard ratio [HR] = 15.057; P = .004). High white blood cell count was not a risk factor for ED (P = .055), but it was for relapse (HR = 2.7; P = .009). FLT3 mutation (HR = 3.9; 95% confidence interval, 1.4 to 10; P = .007) and older age (≥ 60 years) (HR = 5.3; 95% confidence interval, 2.4 to 11; P < .001) were prognostic factors for poorer disease-free and overall survival. Interestingly, CD15 negativity (HR = 0.23; P = .049) was a prognostic factor for relapse. The ED rate was 5.9% (17/288 patients).
CONCLUSION: The perceived impact of the identification of these high-risk factors should be described in order to decide whether any modifications to treatment strategy should be entertained.

Abedin, S. & Altman, J.K. 2016.
"Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia (AML), which presents with a distinct coagulopathy. Therapeutic advances have made APL one of the true success stories in oncology, transforming this once lethal disease into the most curable form of AML. For many patients, cure will now be achieved without the use of chemotherapy. It is hoped that limiting chemotherapy will reduce mortality even further, particularly among more vulnerable older adults whose survival lagged behind that of younger patients. It should be noted that early death persists in patients with APL and continues to negatively affect survival. Further, among survivors treated with chemotherapy or even arsenic trioxide (ATO), there remains the potential for long-term toxicities that must be monitored. Understanding the management of these issues is an important complement to ensure maximal survival for patients with APL."

Other Names for Acute Promyelocytic Leukaemia
The following are some of the names used when referring to acute promyelocytic leukaemia:

- AML M3
- APL
- leukaemia, acute promyelocytic
- M3 ANLL
- myeloid leukaemia, acute, M3

Incidence of Adult Acute Promyelocytic Leukaemia in South Africa
In providing the incidence figures of Leukaemia in South Africa, the outdated National Cancer Registry (2016) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the 'Frequency of Histologically Diagnosed Cancer in South Africa' Section of the Registry .

According to the National Cancer Registry (2016) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2016:

Group - Males 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	264	1:801	0,68%
Asian males	10	1:659	1,02%
Black males	135	1:1 233	1,03%
Coloured males	17	1:1 105	0,33%
White males	102	1:354	0,48%

Group - Females 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	227	1:1 107	0,54%
Asian females	9	1:798	0,72%
Black females	117	1:1 846	0,59%
Coloured females	21	1:844	0,41%
White females	80	1:465	0,49%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2016 was as follows (National Cancer Registry, 2016):

Group - Males 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	156	15	28	20	46	34	53	12
Asian males	1	0	1	1	1	3	2	0
Black males	45	11	22	10	18	15	13	1
Coloured males	1	1	2	3	4	2	4	0
White males	8	3	3	6	23	14	34	11

Group - Females 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	38	26	17	26	31	37	37	15
Asian females	2	0	0	1	2	3	1	0
Black females	31	22	11	12	16	13	10	2
Coloured females	1	3	1	3	2	3	8	0
White females	4	1	5	10	11	18	18	13

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Signs and Symptoms of Promyelocytic Leukaemia (APL)

There are no specific symptoms of acute promyelocytic leukaemia (APL) and the condition can be confused with other common illnesses. In general APL develops very quickly and the symptoms appear over a matter of days or weeks.

Common symptoms include:

- Unusual bleeding and bruising
- Paleness
- Tiredness and breathlessness
- Frequent and persistent infections

These are caused by a lack of healthy red and white cells and platelets in the blood. Bleeding is a serious symptom of APL and needs immediate medical attention.

Other less common symptoms may include:

- Bone pain due to a build-up of cancer cells in the bone marrow
- Swollen glands due to a build-up of cancer cells in the lymph nodes
- Abdominal pain due to a swollen liver or spleen

Some people with APL may also develop small lumps on their skin, called chloromas, but this is very uncommon. These form when leukaemia cells cluster under the skin. Very few people experience symptoms such as dizziness and bad circulation. This happens when leukaemia cells interfere with the blood supply to the central nervous system. (Ferri, *et al.*, 2005).

People with APL may experience all, or just some, of these symptoms.

Diagnosis of Promyelocytic Leukaemia

In addition to the standard diagnostic procedures in patients with acute leukaemia, specific APL analyses may be required to confirm the diagnosis.

A diagnosis can be confirmed by means of:

- Case history and physical examination (with special attention to bleeding tendency, anaemic symptoms and infections)
- Complete full blood count, including leukocyte count with differential cell counts
- Bone-marrow aspirate including:
    - Cytology
    - Cytochemistry
    - Immunophenotyping
    - FISH (t(15;17)) or immunofluorescence (PML)
    - Cytogenetics (conventional)
- Bone-marrow histology in case of *punctio sicca* (where the aspiration gives no blood cells)
- Coagulation status including Quick's test (a one-step test for the amount of prothrombin present in blood plasma and for determination of prothrombin clotting time), PTT (a performance indicator measuring the efficacy of both the 'intrinsic' and the common coagulation pathways), fibrinogen, D-dimers (D-dimer tests are ordered, along with other laboratory tests and imaging scans, to help rule out the presence of a thrombus or blood clot. Some of the conditions that the d-dimer test is used to help rule out include deep vein thrombosis, pulmonary embolism and strokes)

Additional diagnostic procedures may include:

- General health condition by means of the ECOG/WHO Score [The Eastern Cooperative Oncology Group (ECOG) score (published by Oken *et al.* in 1982), also called the WHO or Zubrod score (after C Gordon Zubrod). It runs from 0 to 5, with 0 denoting perfect health and 5 death]
- Evaluation of co-morbidities
- Clinical chemistry, urine analysis
- Hepatitis and HIV serology

- Pregnancy test (if applicable)
- Chest X-ray
- Electrocardiogram (ECG)
- Echocardiography (in case of previous cardiac disease)

Labrador, J., Luño, E., Vellenga, E., Brunet, S., González-Campos, J., Chillón, M.C., Holowiecka, A., Esteve, J., Bergua, J., González-Sanmiguel, J.D., Gil, C., Tormo, M., Salamero, O., Manso, F., Fernández, I., de laSerna, J., Moreno, M.J., Pérez-Encinas, M., Krsnik, I., Ribera, J.M., Cervera, J., Calasanz, M.J., Boluda, B., Sobas, M., Lowenberg, B., Sanz, M.A. & Montesinos, P. 2018.
"Although additional cytogenetic abnormalities (ACA) do not affect the prognosis of patients with t(15;17) acute promyelocytic leukemia (APL), the role of a complex karyotype (CK) is yet to be clarified. We aimed to investigate the relationship of CK with relapse incidence in 1559 consecutive APL patients enrolled in three consecutive trials. Treatment consisted of AIDA induction followed by risk-adapted consolidation. A CK (CK) was defined as the presence of ≥2 ACA, and a very CK (CK+) as ≥3 ACA. Eighty-nine patients (8%) had a CK, of whom 41 (4%) had CK+. The 5-year cumulative incidence of relapse (CIR) in patients with CK was 18%, and 12% in those with <2 ACA (p=.09). Among patients with CK+, the 5-year CIR was 27% vs 12% (p=.003), retaining the statistical significance in multivariate analysis. This study shows an increased risk of relapse among APL patients with CK + treated with ATRA plus chemotherapy front-line regimens."

Treatment of Promyelocytic Leukaemia
Treatment for patients with acute promyelocytic leukaemia (APL), the M3 subtype of acute myeloid leukaemia (AML), usually differs from treatment for patients with other AML subtypes. APL is one of the most frequently cured AML subtypes.

- All-*Trans* Retinoic Acid - All-*trans* retinoic acid (ATRA. It is said that at least 80 percent of patients undergo short-term remission when ATRA is used alone.
- About 70 percent to 80 percent of APL patients go into remission after being treated with ATRA and an anthracycline.
- Patients in remission usually get long-term follow-up care to determine whether they are cured or need further therapy.
- Arsenic Trioxide - the drug arsenic trioxide (ATO) (Trisenox®) is sometimes given to APL patients.

Efficace, F., Breccia, M., Avvisati, G., Cottone, F., Intermesoli, T., Borlenghi, E., Carluccio, P., Rodeghiero, F., Fabbiano, F., Luppi, M., Romani, C., Sborgia, M., D'Ardia, S., Nobile, F., Cantore, N., Crugnola, M., Nadali, G., Vignetti, M., Amadori, S. & Lo Coco. F. 2018.
"The objective of this study was to investigate health-related quality of life (HRQOL), symptom burden, and comorbidity profile in long-term acute promyelocytic leukemia (APL) survivors treated with standard chemotherapy. Overall, 307 long-term APL survivors were invited to participate. HRQOL was assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and compared with that of age and sex-matched controls from the general population. Symptom burden was assessed with the MD Anderson Symptom Inventory (MDASI) questionnaire and comorbidity profile was also investigated. Median follow-up time since diagnosis was 14.3 years (interquartile range: 11.1-16.9 years). APL survivors had a statistically and clinically meaningful worse score for the role physical scale of the SF-36 (-9.5; 95% CI, -15.7 to -3.2, P = 0.003) than their peers in the general population. Fatigue was reported as moderate to severe by 29% of patients and

84.4% reported at least one comorbidity. Prevalence of comorbidity in APL survivors was higher than that reported by the general population. Also, marked variations were found in the HRQOL profile by number of comorbidities. Even many years after treatment ends, APL survivors treated with standard chemotherapy do not fully recover as they report HRQOL limitations and a substantial burden of symptoms."

Prognosis (Outlook) of Promyelocytic Leukaemia

The overall prognosis for adults with APL is better than for patients with other forms of acute myeloblastic leukaemia (AML), although it still depends to some extent on individual patient-specific factors (e.g. age, general fitness) and on features of the disease (e.g. whether it is M3v or PML/RARαnegative).

Almost all patients can expect to achieve a good first remission.

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INTRODUCTION: Although a considerable improvement in survival of patients with acute promyelocytic leukemia (APL) has been seen over the past decades, real-life outcomes seem to be worse than those reported by prospective studies. We aim to describe clinical characteristics and outcomes of adult patients diagnosed with APL in an academic hospital from the University of Sao Paulo.

PATIENTS AND METHODS: We retrospectively reviewed the medical charts of 61 patients with APL diagnosed between January 2007 and May 2017. Baseline clinical features and follow-up data were collected, focusing on early toxicity variables such as infection, bleeding, and thrombosis in the first 30 days from diagnosis.

RESULTS: Among the 61 patients with APL, 54 received any chemotherapy. All patients also received all-trans retinoic acid (ATRA). Bleeding events were the main cause of death before receiving chemotherapy. Most patients belonged to the intermediate (43%) and high-risk (41%) groups, according to Sanz score. The '7 + 3 + ATRA' regimen was the most used regimen (n = 38). An early death rate of 20% was found, predominantly owing to sepsis. After a median follow-up of 5 years, only 1 relapse was diagnosed. The overall survival at 5 years was 59%.

DISCUSSION: In comparison with prospective trials with ATRA-based regimens, we found an inferior overall survival, mostly on account of a high early-death rate. Our results are in line with other real-life retrospective reports published in the past decades.

CONCLUSION: Results of real-life studies differ from those found by prospective trials. Accordingly, early actions and supportive care are still needed, aiming to decrease toxicity, especially in developing countries.

Follow-up

The main purpose of follow-up of patients treated for APL is the detection of relapse and of treatment complications. During the first year following completion of chemotherapy, patients are usually checked every one to two months. Checks may then gradually become less frequent until

they are given annually at five years and beyond. Long-term follow-up is particularly important for those patients who have received treatments that may affect the function of their heart.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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"Intravenous arsenic trioxide (ATO) has been adopted as the first-line treatment for acute promyelocytic leukemia (APL). Another arsenic compound named the Realgar-Indigo naturalis formula (RIF), an oral traditional Chinese medicine containing As_4S_4, has been shown to be highly effective in treating adult APL. In the treatment of pediatric APL, the safety and efficacy of RIF remains to be confirmed. This randomized, multicenter, and noninferiority trial was conducted to determine whether intravenous ATO can be substituted by oral RIF in the treatment of pediatric APL. From September 2011 to January 2017, among 92 patients who were 16 years old or younger with newly diagnosed PML-RARa positive APL, 82 met eligible criteria and were randomly assigned to ATO (n = 42) or RIF (n = 40) group. The remaining 10 patients did not fulfilled eligible criteria because five did not accept randomization, four died and one had hemiplegia prior to arsenic randomization due to intracranial hemorrhage or cerebral thrombosis. Induction and consolidation treatment contained ATO or RIF, all-trans-retinoic acid and low intensity chemotherapy. End points included event-free survival (EFS), adverse events and hospital days. After a median 3-year follow-up, the estimated 5-year EFS was 100% in both groups, and adverse events were mild. However, patients in the RIF group had significantly less hospital stay than those in the ATO group. This interim analysis shows that oral RIF is as effective and safe as intravenous ATO for the treatment of pediatric APL, with the advantage of reducing hospital stay. Final trial analysis will reveal mature outcome data."

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"Between April 2004 and December 2010, we conducted a prospective randomized controlled study comparing tamibarotene with all-trans retinoic acid (ATRA) in the maintenance therapy of newly diagnosed acute promyelocytic leukemia (APL), and here report the final results of this study with a

median follow-up of 7.3 years. Of 344 eligible patients who had received ATRA and chemotherapy, 319 (93%) achieved complete remission (CR). After completion of three courses of consolidation chemotherapy, 269 patients in molecular remission underwent maintenance randomization, 135 to ATRA (45 mg/m^2 daily), and 134 to tamibarotene (6 mg/m^2 daily) for 14 days every 3 months for 2 years. The primary endpoint was relapse-free survival (RFS). The 7-year RFS was 84% in the ATRA arm and 93% in the tamibarotene arm ($p = 0.027$, HR = 0.44, 95% CI, 0.21 to 0.93). The difference was prominent in high-risk patients with initial leukocytes $\geq 10.0 \times 10^9$/L (62% vs. 89%; $p = 0.034$). Tamibarotene was significantly superior to ATRA by decreasing relapse in high-risk patients. Overall survival after randomization did not differ (96% vs. 97%; $p = 0.520$). Secondary hematopoietic disorders developed in nine patients, secondary malignancies in 11, and grade 3 or more late cardiac comorbidities in three. These late complications did not differ between the two arms."

Medical Disclaimer

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