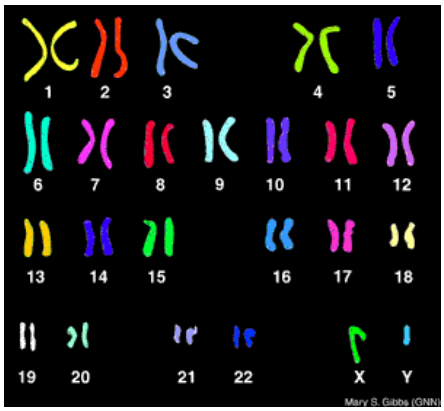
Cancer Association of South Africa (CANSA)

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.

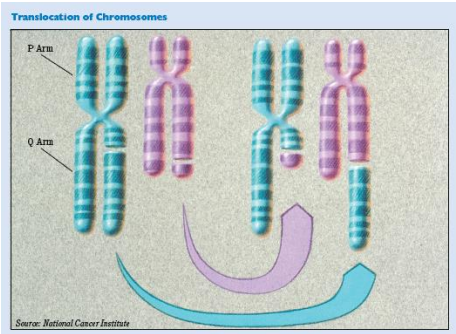


[Picture Credit: Karyotype]

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).

Cingam, S.R. & Koshy, N.V. 2020.

"Acute promyelocytic leukemia is a distinguished subset of acute myeloid leukemia which is characterized by fusion gene transcript PML-RAR-alpha and high cure rates with treatment. This entity was first described in 1957 in patients with severe bleeding tendencies with fibrinolysis, rapid deterioration of the clinical condition, and the presence of promyelocytes in peripheral blood and bone marrow. Advances in the molecular pathology of this leukemia have led to the introduction of arsenic trioxide and all-trans retinoic acid therapies, which have led to improved prognosis."

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Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Jiminez, J.J., Chale, R.S., Abad, A.C. & Schally, A.V. 2020.
"Acute Promyelocytic Leukemia (APL) is characterized by a block in differentiation where leukemic cells are halted at the promyelocyte stage. A characteristic balanced chromosomal translocation between chromosomes 15 and 17 t (15;17) (q24; q21) is seen in 95% of cases - the translocation results in the formation of the PML-RARA fusion protein. The introduction of retinoic acid (RA) and arsenic trioxide (ATO) has been responsible for initially remarkable cure rates. However, relapsed APL, particularly in the high-risk subset of patients, remains an important clinical problem. In addition, despite the success of ATRA & ATO, many clinicians still elect to use cytotoxic chemotherapy in the treatment of APL. Patients who become resistant to ATO have an increased risk of mortality. The probability of relapse is significantly higher in the high-risk subset of patients undergoing treatment for APL; overall approximately 10-20% of APL patients relapse regardless of their risk stratification. Furthermore, 20-25% of patients undergoing treatment will develop differentiation syndrome, a common side effect of differentiation agents. Recent evidence using *in vitro* models has shown that mutations in the B2 domain of the PML protein, mediate arsenic resistance. Alternative agents and approaches considering these clinical outcomes are needed to address ATO resistance as well as the relapse rate in high risk APL."

Thomas, X. & Heiblig, M. 2020.
"Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) cytogenetically characterized by a balanced reciprocal translocation between chromosomes 15 and 17, which results in the fusion between the promyelocytic leukemia (*PML*) gene and retinoic acid receptor-α (*RARα*)/"

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.

Sommer, K., Vignetti, M., Cottone, F., Breccia, M., Annibali, O., Luppi, M., Intermesoli, T., Borlenghi, E., Carluccio, P., Rodeghiero, F., Fabbiano, F., Romani, C., Sborgia, M., Martino, B., Crugnola, M. & Efficace, F. 2020.
Objective: We aimed to investigate the association of fatigue with severity of other key cancer symptoms, as well as symptom interference with daily activities and outlook on life, in long-term survivors of acute promyelocytic leukaemia (APL).
Methods: The study sample consisted of APL survivors (n=244), with a median time from diagnosis of 14.3 years (IQR=11.1-16.9 years), previously enrolled in a long-term follow-up study. Symptom severity and symptom interference were assessed using the well-validated MD Anderson Symptom Inventory (MDASI). Fatigue was evaluated with the Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire.
Results: Higher fatigue burden was associated with increased affective symptoms, memory problems, drowsiness, sleep disturbances, shortness of breath and pain. Higher levels of fatigue were also associated with higher scores across all interference items of the MDASI. Overall, symptoms interfered most with mood, but among APL survivors with high levels of fatigue, symptoms interfered most with enjoyment of life. Multivariable regression analysis confirmed the independent association between fatigue and all symptom severity items of the MDASI.
Conclusions: The current findings show that long-term APL survivors who report higher fatigue also experience a greater overall symptom burden and a substantial impact on performance of daily activities. Further studies are needed to examine whether interventions aimed at reducing fatigue could also reduce overall symptom burden.

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.

Xu, Z-L. & Huang, X-J. 2020.
"The treatment of acute promyelocytic leukaemia (APL) has evolved dramatically over the past several decades, making the disease a highly curable form of acute leukaemia. The discoveries of all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) were landmark events, leading to historic revolutions in the treatment of APL. One major change was from chemotherapy-based to chemotherapy-free treatment regimens, and the combination of ATRA plus ATO without chemotherapy has been recommended as the standard therapy for non-high-risk APL. The other major change was from the intravenous administration of medicine in the hospital to a largely home-based oral approach, which is a more cost-effective and convenient treatment model. In this review, we focus on the evolution of therapeutic approaches for APL, as well as the challenges that remain with the current approaches."

Kumana, C.R., Mak, R., Kwong, Y-L. & Gill, H. 2020.
"Various forms of arsenic were used in China and elsewhere for over 5,000 years. Following the initial success of intravenous arsenic trioxide (i.v. As_2O_3), we revived an oral formulation of pure As_2O_3 in 1998 for the treatment of acute promyelocytic leukemia (APL). We were the first to produce a 1 mg/ml oral-As_2O_3 solution and showed that it had comparable bioavailability to i.v. As_2O_3. Moreover, we also reported that intracellular arsenic concentrations were considerably higher than the corresponding plasma values. Our oral-As_2O_3 was patented internationally and registered in Hong Kong for the treatment of APL. Safety, tolerability and clinical efficacy was confirmed in long-term follow-up studies. We have extended the use of oral-As_2O_3 to frontline induction of newly diagnosed APL. With these findings, we are moving toward an era of completely oral and chemotherapy-free management of APL."

Bankar, A., Korula, A., Kulkarni, U.P., Devasia, A.J., Na, F., Lionel, S., Abraham, A., Balasubramanian, P., Janet, N.B., Nair, S.C.S.S., Jeyaseelan, V., Prasad, J., George, B. & Mathews, V. 2020.
"Arsenic trioxide (ATO)-based regimens are the standard of care for treating acute promyelocytic leukaemia (APL) and have replaced chemotherapy-based approaches. However, the cost of "patented" ATO is prohibitive because of patent rights. "Generic" ATO has been used in a few countries, but its implications for health resource utilization (HRU) and cost of treatment are unknown. We hypothesized that treating APL patients using generic ATO (APL-ATO) will be cost effective compared to the chemotherapy-based regimen (APL-CT). In a single-centre retrospective study, we used a bottom-up costing method to compare the direct medical cost of treatment and HRU between APL-ATO and APL-CT. These costs and the survival and relapse probabilities were imputed in a three-state Markov decision model to estimate the cost effectiveness of APL-ATO compared to APL-CT. The mean cost of treatment for APL-ATO (n = 30, $8500 ± 2078) was significantly less than for APL-CT (n = 30, $22 600 ± 5528) (P < 0·001). APL-ATO reduced hospitalization, antibiotic and antifungal usage (P < 0·001). In the Markov model, five-year treatment costs were significantly lower for APL-ATO ($11 131) than for APL-CT ($17 926) (P < 0·001).

Treatment cost and health resource utilization were significantly lower for generic ATO-treated APL patients compared to the chemotherapy-based regimen."

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.

Silva, W.F.D. Jr., Rosa, L.I.D., Marquez, G.L., Bassolli, L., Tucunduva, L., Silveira, D.R.A., Buccheri, V., Bendit, I., Rego, E.M., Rocha, V. & Velloso, E.D.R.P. 2019.

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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"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

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/ estate/heirs) relating to the use of any information contained in this Fact Sheet.

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any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

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Leukaemia and Lymphoma Society
http://www.lls.org/diseaseinformation/leukemia/acutemyeloidleukemia/treatment/apl/

National Heart, Lung and Blood Institute
http://www.nhlbi.nih.gov/health/health-topics/topics/dic/

National Cancer Institute
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

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