
ATRA and ATO for Acute Promyelocytic Leukaemia (APL)

**A Guide for
Patients**

Introduction

In this booklet, we describe the use of all-trans retinoic acid (ATRA), also known as tretinoin, and arsenic trioxide (ATO) for the treatment of acute promyelocytic leukaemia (APL).

This booklet was originally put together by Saloua Najjam, PhD and peer reviewed by Dr Steve Knapper, University of Wales, Cardiff. It has then been updated by our Patient Information Writer, Isabelle Leach. We are also grateful to leukaemia patients Bruce Bain and John Pointon for their valuable contributions.

If you would like any information on the sources used for this booklet, please email communications@leukaemiacare.org.uk for a list of references.

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About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 8:30am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemicare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who

has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemicare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemicare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemicare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Patient and carer conferences

Our nationwide conferences provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support.

Website

You can access up-to-date information on our website, **www.leukaemicare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemicare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemicare.org.uk/communication-preferences/**

What is ATRA and ATO therapy?

ATRA and ATO therapy is a combination treatment of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) which is now recognised as the first-line treatment for acute promyelocytic leukaemia (APL). A first-line treatment is accepted as the best initial treatment for a given type and stage of a disease.

APL is a rare sub-type of acute myeloid leukaemia (AML) in which there is an increased production of immature, abnormal white blood cells called promyelocytes in the bone marrow. It is a special type of AML in that it is nearly always associated with a specific gene called the PML-RARA (ProMyelocytic Leukaemia-Retinoic Acid Receptor Alpha) gene. When treated with ATRA and ATO, it has an excellent prognosis; better than other sub-types of AML.

The PML-RARA gene is the result of the swapping of the PML gene on chromosome 15 and the RARA gene on chromosome 17 which fuse to become the PML-RARA gene.

ATRA blocks the effect of the PML-RARA gene that prevents the promyelocyte cells maturing into normal white blood cells. Until recently, ATRA, which is an active by-product of vitamin A, was given with chemotherapy drugs called anthracyclines. It was given in combination with an anthracycline to prevent any drug resistance to ATRA. Anthracycline drugs, such as daunorubicin or idarubicin, interfere with the DNA and reproduction of white blood cells, including the leukaemia cells.

In 2018, NICE approved ATO for the first-line treatment of APL in previously untreated patients, with low-to-intermediate risk disease, and patients with APL that was refractory (did not respond to chemotherapy) or patients who had relapsed (APL returned after chemotherapy).

ATRA and ATO are not chemotherapy drugs, but drugs called differentiating agents. They encourage the promyelocytic cells to differentiate (mature) into normal white blood cells. They

also have complementary actions in that ATRA breaks down the PML-RARA gene and ATO encourages the abnormal APL cells to self-destruct.

For further details on the causes, symptoms, diagnosis and clinical features of APL, you can read our booklet on our website at www.leukaemiacare.org.uk. Alternatively, you can order a copy by calling our helpline on **0808 010 444**.

Who receives ATRA and ATO therapy?

Patients suspected of having APL should start ATRA treatment immediately, even before the diagnosis is fully confirmed, because they can quickly develop potentially life-threatening bleeding or blood clotting symptoms. A confirmed diagnosis of APL using genetic testing can be performed later, and treatment can be discontinued if APL is not confirmed.

Based on recent studies comparing ATRA plus ATO with ATRA plus chemotherapy, the European Medicines Agency (EMA) have approved ATO for the treatment of newly diagnosed patients with low-to-intermediate risk APL who are defined as patients with a white blood cell (WBC) count of 10000 cells per microlitre of blood or less. Patients with APL and a WBC count higher than this are considered to be high-risk.

To achieve remission (induction therapy) and re-enforce remission (consolidation therapy):

- Patients with low-to-intermediate risk APL can be given ATRA plus ATO

- Patients with high-risk APL can be given either of the following regimens because studies have shown that neither was superior to the other:

- ATRA plus ATO with cytoreductive chemotherapy such as cytarabine (cytoreductive means that the chemotherapy reduces the number of cells, which in the case of APL are abnormal promyelocytes)
- ATRA plus an anthracycline

However, using ATO for high-risk patients may be difficult because the EMA has only approved ATO for low-to-intermediate risk APL, but not for high-risk APL as of yet.



How is ATRA and ATO therapy administered?

ATRA and ATO therapy should be started as soon as possible and monitored under the supervision of a doctor experienced in the use of chemotherapeutic agents who will explain the use of this combination therapy to you.

Before starting treatment with ATRA and ATO, the following clinical assessments will be carried out:

- Measurement of your weight and height.
- Full blood count, liver function tests, and urea/electrolyte levels as a measure of kidney function. These tests will be performed before each treatment cycle.
- A pregnancy test will be carried out on all female patients of child-bearing age before starting treatment.
- Electrocardiogram (ECG) to check that your heart is working normally.
- Bone marrow biopsy to check how many cancer cells there are in your bone marrow. In a bone marrow biopsy, a sample of

bone marrow is collected from the chest or hip bone, generally under local anaesthetic, using a bone marrow surgical instrument. The sample is then examined for abnormal cells.

You will then need to read and sign a consent form summarising the receipt of verbal and written information about your disease, treatment and potential side effects.

All patients will start induction treatment as an inpatient but very few will remain inpatients all the way through the eight weeks it takes to deliver ATO induction. The latter part of these weeks will be given to you as an outpatient once you are completely stable and responding well to treatment.

Depending on the Haematology Unit in your hospital, you will probably be able to have consolidation treatment on an outpatient basis. As this is a combination treatment, your consultant will decide the best combination regimen in terms of the doses and the frequency of administration for you. As an

outpatient, you may be told to monitor your temperature as this can be a sign of infection. If your temperature is above 37.5°C, then please contact your doctor or nurse.

In addition to induction treatment, patients with APL require supportive care such as blood product transfusions to maintain the platelet count and the blood clotting indicators as normal as possible. Blood chemical levels (particularly potassium and magnesium which are important for electrical conduction in the heart) will be monitored closely. Sometimes it is necessary to also give potassium and/or magnesium supplements.

For consolidation treatment, patients will be given seven courses of ATRA (with a two-week break between courses) and four consolidation courses of ATO (with a four-week break between courses) are recommended by the latest guidelines.

What are the side effects of ATRA and ATO therapy?

Everyone will experience different side effects with ATRA and ATO therapy. However, because they have a high white blood cell count, high-risk patients are more likely to experience side effects. It is important to report side effects to your doctor or nurse so that they can be managed and treated differently. The most common side effects when ATRA and ATO are given together are shown below.

Side effects in patients with APL treated with ATRA or ATO are similar and include:

Differentiation syndrome

This occurs during the first weeks of treatment when the differentiating agents ATRA and ATO start allowing the promyelocyte cells to mature. It is usually associated with a rise in the white blood cell count. Differentiation syndrome can usually be treated with steroids. Symptoms include:

- Fever, cough, fluid in the lungs and difficulty breathing
- Fluid in the tissues and kidney damage

- Weight gain

Pseudotumour cerebri

This non-serious increase in pressure in the skull is seen with both ATRA and ATO, and is more common when both drugs are given together. It can be treated with steroids and by decreasing the dose of ATRA. Symptoms include:

- Headaches and dizziness
- Eye problems, including swelling of the optic disk and/or double vision
- Confusion

Heart rhythm disturbance (prolongation of the QT interval) which can be seen on the ECG

Treatment may cause heart problems, especially for patients with existing heart disease. ECG monitoring before and twice a week throughout treatment is recommended. Patients with this condition should have treatment stopped and then restarted when the heart rhythm disturbances subside.

Other side effects include:

- Harmful liver effects.
- Changes to mood: Confusion, anxiety and depression.
- Fatigue: Normally mild, you can feel you have a lack of energy. Also, you may feel tiredness and weakness.
- Nausea and vomiting: This can be easily managed with anti-sickness medication.
- Diarrhoea and/or constipation.
- Changes to skin: problems with your skin can include rashes, dry skin, itching and your skin tone appearing flushed.
- Bone and muscle pain.
- Numbness and tingling in fingers and toes.

ATO is also linked to excess of glucose and changes in mineral levels in the blood. From ATO therapy, you may also experience swelling of the hands and feet, due to a build-up of fluid.

ATRA is also linked to a loss of appetite, difficulty sleeping, dry mouth and nose, inflammation

of the pancreas/abdominal pain, inflammation of the lips, hair loss, increased sweating and chills.

Fertility, pregnancy and breastfeeding

There are no animal or human studies into the effect of ATO or ATRA on fertility.

There are no studies into the use of ATO or ATRA in pregnant women. However, ATRA is a retinoid, and other retinoid drugs are known to cause abnormalities to the baby when exposed to the drugs during pregnancy. ATO has been shown to cause abnormalities for the baby in animal studies. Women receiving ATO or ATRA are therefore advised to avoid pregnancy by using effective contraception during and for at least one month after finishing treatment with ATO or ATRA.

Women who are taking ATO or ATRA are advised not to breastfeed.

What happens if ATRA and ATO therapy doesn't work?

For patients with APL who have had an early diagnosis and been treated without delay, excellent cure rates of over 90% for low-to-intermediate risk patients and 85% for high-risk patients have been reported.

If following your treatment with ATRA and ATO, your APL has not gone into remission or you

have relapsed after achieving remission, your consultant is the best person to discuss what other treatments are available, and help you decide the next course of action. Knowledge of your genetic results, your physical condition and any new treatments which may help you will guide your consultant's recommendations.

Leukaemia Care offers nationwide support groups for people affected by a diagnosis of a blood or lymphatic cancer. Visit www.leukaemiacare.org.uk, or call **08088 010 444**, to find out more and to find a group near you.

Glossary

Acute Myeloid Leukaemia (AML)

A rapid and aggressive cancer of the myeloid cells in the bone marrow.

Amino Acids

Organic molecules which are the building blocks for making proteins.

Anthracyclines

An antibiotic derived from the bacteria *Streptomyces peucetius* and found to be an effective anticancer drug.

Autologous Stem Cell Transplant

A transplant of stem cells derived from part of the same individual.

Bone Marrow

The soft blood-forming tissue that fills the cavities of bones and contains fat, immature and mature blood cells, including white blood cells, red blood cells and platelets.

Bone Marrow Biopsy

A collection of a sample of bone marrow from the hip bone, generally under local anaesthetic. A bone marrow surgical instrument with a cylindrical blade, called a trephine, is used to remove a one to two-centimetre core of bone marrow in one piece.

Bone Marrow Failure

The term used when the bone marrow is unable to keep up with the body's need for white and red blood cells and platelets.

Chemotherapy

Drugs that work in different ways to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Chromosomes

Thread-like structures which carry the genes, and are located in the nuclei of every cell in the body. There are 46 chromosomes (23 pairs) in humans.

Glossary (cont.)

Complete Remission

Complete remission has occurred when:

- Blood cell counts have returned to normal
- Less than 5% of abnormal, leukaemia cells are still present in the bone marrow

Consolidation Treatment

Treatment following remission intended to kill any cancer cells that may be left in the body.

DNA (Deoxyribonucleic Acid)

A thread-like chain of amino acids found in the nucleus of each cell in the body which carries genetic instructions used in the growth, development and functioning of the individual's cells.

Electrocardiogram (ECG)

The test that records the electrical signals in your heart to detect any heart problems and monitor the heart's status.

Electrolytes

Salts and minerals in the blood

that help conduct electrical impulses in the body. They include sodium, potassium, chloride and bicarbonate among others.

First-line Treatment

The first treatment given for a disease. It is generally the treatment accepted by the medical profession as the best initial treatment for a given type and stage of cancer.

Genes

Genes are made up of DNA which stores the genetic information required to make human proteins.

Induction Treatment

The first treatment after diagnosis intended to kill the majority of the leukaemia cells and stimulate remission.

Leukaemia

A group of cancers that usually begin in the bone marrow and result in high numbers of abnormal blood cells. These cells are not fully developed and are called blasts or leukaemia cells.

Depending on the type of blood cell involved, there are different types of leukaemia with varying characteristics, such as being acute (develops quickly) or chronic (develop slowly).

Maintenance

The treatment given to prevent cancer from coming back after it has disappeared following first-line treatment.

Myeloid

Relates to the bone marrow.

Platelets

One of the types of blood cells which help to stop bleeding.

Red Blood Cells

The small blood cells that contain haemoglobin and carry oxygen and other substances to all tissues of the body.

Refractory Condition

A condition for which treatment does not result in a remission. However, the condition may be stable.

Relapse Condition

Relapse occurs when a patient initially responds to treatment, but after six months or more, the response stops. This is also sometimes called a recurrence.

Stem Cell

The most basic cell in the body that has the ability to develop into any of the body's specialised cell types, from muscle cells to brain cells. However, what make these stem cells reproduce uncontrollably, as in cancer, is thought to be linked to chromosome abnormalities.

Stem Cell Transplantation

The transplant of stem cells derived from part of the same individual or a donor.

Urea

The breakdown product of proteins in the body which is excreted in the urine.

White Blood Cells

White blood cells are one of the types of cells found in the blood

Glossary (cont.)

and bone marrow, along with red blood cells and platelets. White blood cells create an immune response against both infectious disease and foreign invaders. Granulocyte white blood cells include the neutrophils (protect against parasites and allergens) and basophils (create the inflammatory reactions during an immune response). Other white blood cells include the lymphocytes (recognise bacteria, viruses and toxins, to which they produce antibodies) and monocytes (clear infection products from the body).

For more definitions of terms that you may come across during your blood cancer journey, you can download our booklet A to Z of Leukaemia from our website at www.leukaemiacare.org.uk

Useful contacts and further support

There are a number of helpful sources to support you during your diagnosis, treatment and beyond, including:

- Your haematologist and healthcare team
- Your family and friends
- Your psychologist (ask your haematologist or CNS for a referral)
- Reliable online sources, such as Leukaemia Care
- Charitable organisations

There are a number of organisations, including ourselves, who provide expert advice and information.

Leukaemia Care

We are a charity dedicated to supporting anyone affected by the diagnosis of any blood cancer.

We provide emotional support through a range of support services including a helpline, patient and carer conferences, support group, informative website, one-to-one buddy service and high-quality patient information. We also have a nurse on our help line for any medical queries relating to your diagnosis.

Helpline: **08088 010 444**
www.leukaemicare.org.uk
support@leukaemicare.org.uk

Blood Cancer UK

Blood Cancer UK is the leading charity into the research of blood cancers. They offer support to patients, their family and friends through patient services.

0808 169 5155
www.bloodcancer.org.uk

Cancer Research UK

Cancer Research UK is a leading charity dedicated to cancer research.

0808 800 4040
www.cancerresearchuk.org

Macmillan

Macmillan provides free practical, medical and financial support for people facing cancer.

0808 808 0000
www.macmillan.org.uk

Maggie's Centres

Maggie's offers free practical, emotional and social support to people with cancer and their families and friends.

0300 123 1801
www.maggiescentres.org

Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

08444 111 444
www.adviceguide.org.uk

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**

(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemicare.org.uk

support@leukaemicare.org.uk

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Leukaemia Care is registered as a charity in England and Wales (no.1183890) and Scotland (no. SC049802).
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Leukaemia Care
YOUR Blood Cancer Charity