Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Adult Acute Lymphoblastic Leukaemia (ALL)

Introduction

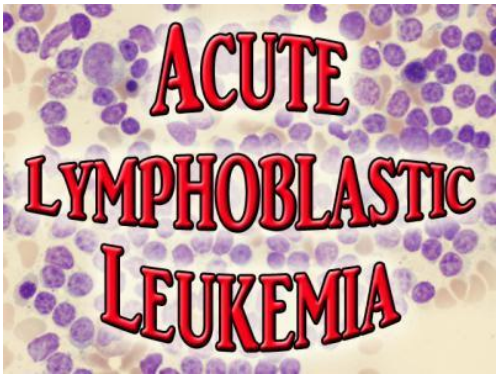
The word *leukaemia* literally means 'white blood' and is used to describe a variety of cancers that begin in the blood-forming cells (lymphocytes) of the bone marrow.

Leukaemias are divided into two major types:

- Acute Leukaemia which progresses quickly with many immature white cells
- Chronic Leukaemia which progresses more slowly and has more mature white cells

Both leukaemia and lymphomas (Hodgkin's disease and non-Hodgkin's lymphomas) are cancers of lymphocytes. The difference is that leukaemia starts in the bone marrow while lymphomas originate in lymph nodes and then spread to the bone marrow or other organs.

[Picture Credit: ALL]



White blood cells (*leukocytes*) evolve from immature cells referred to as *blasts*. Malignancy of these blast cells is the source of leukaemias, which generally progress as follows:

- Normally, blasts constitute 5% or less of healthy bone marrow. In leukaemia, however, these blasts remain immature and multiply continuously but fail to mature properly, eventually constituting between 30 - 100% of the bone marrow.
- In time, these malignant blast cells fill up the bone marrow and prevent production of healthy red cells, platelets and mature white cells (leukocytes).
- Malignant blasts spill out of the marrow into the bloodstream and lymph system and can travel to the brain and spinal cord (the central nervous system). Some blasts are called *lymphoblasts* (which normally become mature cells called *lymphocytes*) and others are called *myeloblasts* (which mature to *myeloid* cells).

(University of Maryland Medical Center).

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

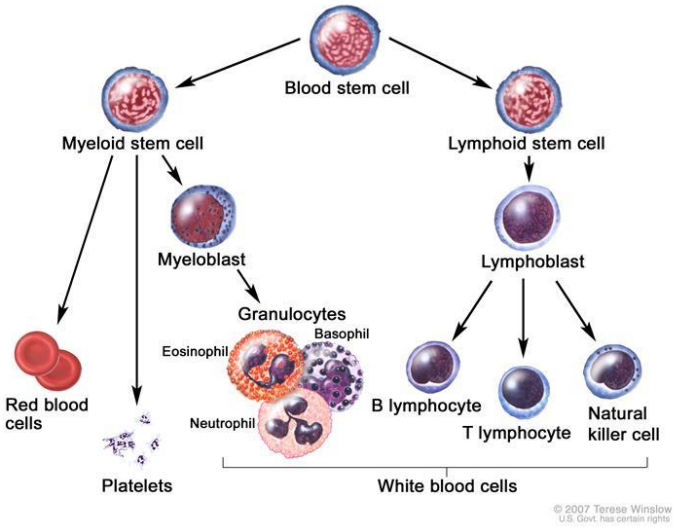
Adult Acute Lymphoblastic Leukaemia

Adult acute lymphoblastic leukaemia (ALL) is a type of cancer in which the bone marrow makes too many lymphocytes (a type of white blood cell). It is also called acute lymphocytic leukaemia, a cancer of the blood and bone marrow. This type of cancer usually gets worse quickly if it is not treated.

Normally, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell.

A myeloid stem cell becomes one of three types of mature blood cells:

- Red blood cells that carry oxygen and other substances to all tissues of the body
- Platelets that form blood clots to stop bleeding
- Granulocytes (white blood cells) that fight infection and disease



[Picture Credit: Blood Cell Development]

A lymphoid stem cell becomes a lymphoblast cell and then one of three types of lymphocytes (white blood cells):

- B lymphocytes that make antibodies to help fight infection
- T Lymphocytes that help B lymphocytes make the antibodies that help fight infection
- Natural killer cells that attack cancer cells and viruses

Anything that increases one's risk of getting a disease is called a risk factor. Having a risk factor does not mean that one will get cancer and not having risk factors doesn't mean that one will not get cancer.

Talk with a doctor if there is suspicion of the presence of any possible risk factors. Possible risk factors for ALL include the following:

- Being male
- Being white
- Being older than 70
- Having a history of past treatment with chemotherapy or radiation therapy
- Being exposed to radiation from an atomic bomb
- Having certain genetic disorders, such as Down syndrome

(National Cancer Institute).

[Picture Credit: Atom Bomb]

Incidence of Adult Acute Lymphoblastic Leukaemia in South Africa

In providing the incidence figures of Leukaemia in South Africa, The National Cancer Registry (2013) 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.

According to the National Cancer Registry (2013) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	351	1:645	1,98%
Asian males	8	1:907	1,00%
Black males	184	1:1 081	1,71%
Coloured males	46	1:441	1,10%
White males	114	1:282	0,56%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	279	1:1 068	0,76%
Asian females	6	1:1 625	0,60%
Black females	141	1:1 695	0,90%
Coloured females	42	1:722	1,03%
White females	91	1:394	0,57%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	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	103	28	24	42	42	51	39	12
Asian males	3	1	1	0	1	2	0	0
Black males	65	19	15	28	18	15	10	1
Coloured males	14	3	2	4	6	8	4	1
White males	12	5	6	18	18	23	30	11

Group - Females 2013	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	55	34	28	30	45	35	29	16
Asian females	3	0	0	1	0	1	0	1
Black females	28	26	21	13	16	14	7	4
Coloured females	5	4	3	9	10	4	2	2
White females	14	3	4	7	18	13	20	8

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.

Risk Factors for Adult Acute Lymphoblastic Leukaemia

There are only a few known risk factors for acute lymphocytic leukaemia (ALL). The following are risk factors for adult acute lymphoblastic leukaemia:

Radiation exposure - being exposed to high levels of radiation is a risk factor for both ALL and acute myeloid leukaemia (AML). Japanese atomic bomb survivors had a greatly increased risk of developing acute leukaemia, which occurs usually within 6 to 8 years after the original exposure.

Treating cancer with radiation therapy also increases the risk for leukaemia, although AML is more often seen than ALL. The risk seems to be higher if chemotherapy and radiation are both used in treatment.

The possible risks for leukaemia by being exposed to lower levels of radiation, such as from medical imaging tests (such as X-rays) are not well known. Exposure of a foetus to radiation within the first months of development may carry an increased risk for leukaemia, but the extent of the risk is not clear. Women should report that they are pregnant if this is known to them.

If there is an increased risk from lower levels of radiation it is likely to be small, but to be safe, most doctors try to limit a person's exposure to radiation as much as possible.

Exposure to Certain Chemicals - the risk of ALL may be increased by exposure to certain chemotherapy drugs and certain chemicals, including benzene and other solvents. Benzene is a solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries, and is also present in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers. Chemical exposure is more strongly linked to an increased risk of AML than to ALL.

The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a human carcinogen that causes nasopharyngeal cancer and also concluded that there is ''strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde''.

Exposure to benzene - exposure to a chemical called benzene at work increases the risk of developing ALL. Exposure to benzene may occur in petrol, chemical, pharmaceutical and rubber industries. Benzene is also used in shoe production and the printing industry. The higher the level of exposure over many years, the greater the risk. There is benzene in traffic pollution but the levels are likely to be too low to increase leukaemia risk. Benzene is also in cigarette smoke (see below).

Smoking and coffee - a review of studies (meta analysis) in 2009 has shown that smoking in the home by parents may increase the risk of ALL in their children. This includes smoking by the father in the time before conception. Data from the French ESCALE study in 2013 suggests that drinking more than 2 cups of coffee a day may slightly increase the risk of childhood ALL. More research is, however, needed on this.

Certain Viral Infections - infection with the human T-cell lymphoma/leukaemia virus-1 (HTLV-1) can cause a rare type of T-cell acute lymphocytic leukaemia. Most cases occur in Japan and the Caribbean area.

In Africa, the Epstein-Barr virus (EBV) has been linked to Burkitt lymphoma, as well as to a form of acute lymphocytic leukaemia. Research has identified viruses, such as HTLV1, and HIV, as potential causes in some cases.

Human T-cell Lymphotropic virus or Human T-lymphotropic virus Type 1 (HTLV-I), also called the Adult T-cell lymphoma virus type 1 is a retrovirus that has been implicated in several kinds of diseases including very aggressive adult T-cell lymphoma (ATL), HTLV-1-associated myelopathy uveitis, strongyloides stercoralis hyper-infection and some other diseases. However only about 1–5% of infected persons are thought to develop cancer as a result of the infection with HTLV-I over their lifetime.

Inherited syndromes - acute lymphocytic leukaemia does not appear to be an inherited disease. It does not seem to run in families, so a person's risk is not increased if a family member has the disease. But there are some inherited syndromes with genetic changes that seem to raise the risk of ALL.

These include:

- Down syndrome
- Klinefelter syndrome
- Fanconi anaemia
- Bloom syndrome
- Ataxia-telangiectasia
- Neurofibromatosis

Race/ethnicity - acute lymphocytic leukaemia is more common in whites than in African Americans, but the reasons for this are not clear. According to statistics in the 2005 South African National Cancer Registry it would appear that this also applies to White men in South Africa.

Sex - acute lymphocytic leukaemia is slightly more common in males than in females. The reason for this is unknown. According to statistics in the 2005 South African National Cancer Registry it would appear that this also applies in South Africa.

Having an identical twin with ALL - someone who has an identical twin who develops ALL in the first year of life has an increased risk of getting ALL.

[Picture Credit: Identical Twins]

Electromagnetic fields - one may read in the press from time to time that some people are concerned about power lines and risk of cancer. Power lines produce high levels of 'low frequency electromagnetic radiation' (EMR).

Although some studies seem to suggest that exposure to very high levels of EMR could increase childhood leukaemia risk, the findings are not very clear. We do not really know if the childhood leukaemia in these studies was actually caused by low frequency EMR. It could be due to some other common factors, or even chance. Scientists agree that more research is needed before one can say for sure one way or the other.

[Picture Credit: Obesity]

Being overweight - some studies show that people who are very overweight (obese) have a slightly higher risk for leukaemia than people with a normal bodyweight.

Paint exposure - one study has shown a slightly higher risk for childhood ALL after exposure to paints, but more studies are needed to back up this finding.

Weakened immunity - an overview study (combined analysis) looked at published research into people with HIV or AIDS, or people treated with medicines that lower immunity after an organ transplant. The researchers found that these people have a risk for leukaemia that is double or triple that of people without these factors.

Uncertain, unproven or controversial risk factors - other factors that have been studied for a possible link to ALL include:

- Exposure to electromagnetic fields (such as living near power lines or using cell phones)
- Workplace exposure to diesel, gasoline, pesticides, and certain other chemicals
- Smoking
- Exposure to hair dyes

So far, none of these (uncertain, unproven or controversial) factors have been linked conclusively to ALL. Research in these areas continues.
(American Cancer Society; Cancer Research UK; MacMillan Cancer Support; NHS Choices; Center for Environmental Health Studies; Zhang, *et al*.).

Philadelphia Chromosome Positive ALL
The Philadelphia Chromosome is a genetic abnormality that was first identified in chronic myelogenous leukemia (CML), but is also seen in over 20% of adult ALL cases. Philadelphia Chromosome positive ALL (Ph+ ALL) has long carried the poorest prognosis of all ALL types, but the discovery of a class of medications that target this genetic abnormality has brought new hope to these patients. The first and most widely studied drug in this class is imatinib. Studies found that imatinib alone did not improve outcomes (in most patients), but that in combination with chemotherapy, results were promising. The best combination and schedule for these medications has not yet been determined. Of note, in elderly patients, studies found imatinib alone to be superior to chemotherapy.

Unlike in CML treatment, imatinib is not a potential cure for Ph+ ALL or effective long-term treatment, but it can induce a temporary remission, and in patients who receive an autologous stem cell transplant, the addition of imatinib improves overall survival.
(Oncolink).

Signs and Symptoms of Adult Acute Lymphoblastic Leukaemia

[Picture Credit: Petechiae]

Signs and symptoms of acute lymphocytic leukaemia may include:

- Bleeding from the gums
- Easy bruising or bleeding
- Petechiae (flat, pinpoint spots under the skin caused by bleeding)
- Bone pain
- Pain or feeling of fullness below the ribs
- Pain in the bones or joints
- Fever or night Sweats
- Frequent infections
- Frequent or severe nosebleeds
- Lumps caused by swollen lymph nodes in and around the neck, underarm, abdomen or groin which are usually painless
- Pale skin
- Shortness of breath
- Weakness, fatigue or a general decrease in energy
- Weight loss and loss of appetite
- Leukaemia cells that spread to the brain and spinal cord can cause:
  - Severe and persistent headache
  - Seizures
  - Trouble with balance

(Mayo Clinic; Cleveland Clinic; National Cancer Institute; Harvard Health Publications).

Diagnosis of Adult Acute Lymphoblastic Leukaemia

Blood specimens are taken and sent to the laboratory for diagnosis.

Different leukaemias are diagnosed according to the type of white blood cell affected and the speed with which the cancer progresses.

Adult acute lymphoblastic leukaemia is an acute leukaemia meaning that it is more aggressive and progresses quickly. It affects a type of white blood cell called lymphoid cells.

The following tests and procedures may be used:

- Physical exam and history: An exam of the body to check general signs of health, including checking for signs of disease, such as infection or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

- Complete blood count (CBC): A procedure in which a sample of blood is drawn and checked for the following:
  - The number of red blood cells and platelets.
  - The number and type of white blood cells.
  - The amount of haemoglobin (the protein that carries oxygen) in the red blood cells.
  - The portion of the blood sample made up of red blood cells.

- Blood chemistry studies: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that makes it.

- Peripheral blood smear: A procedure in which a sample of blood is checked for the presence of blast cells, number and kinds of white blood cells, the number of platelets, and changes in the shape of blood cells.
- Bone marrow aspiration and biopsy: The removal of bone marrow, blood, and a small piece of bone by inserting a hollow needle into the hipbone or breastbone. A pathologist views the bone marrow, blood, and bone under a microscope to look for abnormal cells.

- The following tests may be done on the samples of blood or bone marrow tissue that are removed:

    - Cytogenetic analysis: A laboratory test in which the cells in a sample of blood or bone marrow are looked at under a microscope to find out if there are certain changes in the chromosomes in the lymphocytes. For example, sometimes in ALL, part of one chromosome is moved to another chromosome. This is called the Philadelphia chromosome. Other tests, such as fluorescence in situ hybridisation (FISH), may also be done to look for certain changes in the chromosomes
    - Immunophenotyping: A process used to identify cells, based on the types of antigens or markers on the surface of the cell. This process is used to diagnose the subtype of ALL by comparing the cancer cells to normal cells of the immune system. For example, a cytochemistry study may test the cells in a sample of tissue using chemicals (dyes) to look for certain changes in the sample. A chemical may cause a colour change in one type of leukaemia cell but not in another type of leukaemia cell.

(Leukaemia and Lymphoma Research; Cleveland Clinic).

Staging of Adult Acute Lymphoblastic Leukaemia

Once adult ALL has been diagnosed, tests are done to find out if the cancer has spread to the central nervous system (brain and spinal cord) or to other parts of the body.

The extent or spread of cancer is usually described as stages. It is important to know whether the leukaemia has spread outside the blood and bone marrow in order to plan treatment. The following tests and procedures may be used to determine if the leukaemia has spread:

- Chest x-ray: An X-ray of the organs and bones inside the chest. An X-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body

- Lumbar puncture: A procedure used to collect cerebrospinal fluid from the spinal column. This is done by placing a needle into the spinal column. This procedure is also called an LP or spinal tap
- CT scan (CAT scan): A procedure that makes a series of detailed pictures of the abdomen, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography

- MRI (magnetic resonance imaging): A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI)

(Cleveland Clinic).

Prognosis (Outlook) for Adult Acute Lymphoblastic Leukaemia

The outlook for adult acute lymphoblastic leukaemia depends on factors such as:

- The age of the patient. Younger patients tend to have a better outlook
- Laboratory test results. For example, the outlook is better if the patient has a lower white blood count when originally diagnosed
- The subtype of ALL the patient was diagnosed with (B-cell ALL or T-cell ALL)
- Whether or not the patient has a chromosome abnormality called the Philadelphia chromosome. Having it suggests a poorer prognosis
- The patient's response to chemotherapy. The outlook is better if the patient has no evidence of leukaemia four to five weeks after starting treatment

(WebMD).

Treatment of Adult Acute Lymphoblastic Leukaemia

The treatment for acute lymphoblastic leukaemia varies depending on:

- The type of ALL
- The general health of the patient
- The age and level of fitness of the patient

Different types of ALL may be treated differently. Researchers and doctors continue to look for better combinations of treatments, as well as new treatments. They test these in clinical trials. The doctor may suggest that a patient joins a trial.

Immunotherapy - A single cycle of the CD19-based immunotherapy blinatumomab resulted in complete minimal residual disease (MRD) response in 78% of patients with acute lymphoblastic leukaemia (ALL). A complete MRD response occurred in 80% of patients throughout the course of blinatumomab therapy.

Several different types of immunotherapy are currently being explored for the treatment of leukaemia. They fall into several broad categories, including adoptive cell therapy, monoclonal antibodies, checkpoint inhibitors, therapeutic vaccines, adjuvant immunotherapies, and cytokines.

Adoptive cell therapy is a type of immunotherapy in which immune cells are removed from a patient, grown or genetically modified in lab, and then given back to the patient, often in vastly increased numbers.

Monoclonal antibodies are molecules, generated in the lab, that target specific antigens on tumours. Many monoclonal antibodies are currently used in cancer treatment, and some appear to generate an immune response. Several monoclonal antibodies are currently being tested in clinical trials.

Checkpoint inhibitors is a potentially promising avenue of treatment in leukaemia. These drugs work by targeting molecules that serve as checks and balances in the regulation of immune responses. By blocking inhibitory molecules or, alternatively, activating stimulatory molecules, these treatments are designed to unleash or enhance pre-existing anti-cancer immune responses.

Therapeutic vaccines are designed to elicit an immune response against tumour-specific or tumour-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens.

Adjuvant immunotherapy. Adjuvants are substances that are either used alone or combined with other immunotherapies to boost the immune response.

Cytokines are messenger molecules that help control the growth and activity of immune system cells.
(Cancer Research Institute).

Targeted Therapy - The U.S. Food and Drug Administration (FDA) approved the anti-cancer drug Besponsa (inotuzumab ozogamicin) to treat B-cell Acute Lymphoblastic Leukaemia (ALL).

Besponsa was evaluated in clinical studies involving 326 people with relapsed or refractory B-cell ALL who had received one or two prior treatments with other medication. More than 35 percent of people evaluated achieved complete remission for about eight months after taking Besponsa, compared with about 17 percent of those who took a different chemotherapy drug. Common side effects of Besponsa included low blood platelets, low white-blood-cell count, infection, anaemia, fatigue and severe bleeding.
(MedicineNet).

The phases of treatment for ALL - doctors divide treatment for adult acute lymphoblastic leukaemia into different phases:

- remission induction
- consolidation
- maintenance

This treatment usually takes 2 years. The maintenance treatment takes up most of this time. It is a long time to have treatment. The good news is that most people do very well with treatment.

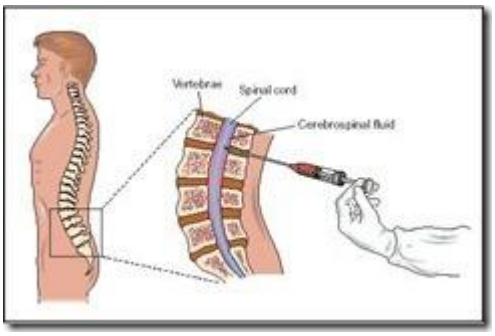
Getting Rid of ALL (remission induction) - the aim of the first phase of treatment is to destroy the leukaemia cells. In remission, there are no leukaemia cells in the blood or bone marrow. Doctors call this first phase of treatment remission induction. The patient usually needs to stay in hospital for about a month.
Before starting the chemotherapy, the patient may need to have blood or platelet transfusions. Then he/she receives treatment with chemotherapy and usually, steroids. They usually have a number of chemotherapy drugs over a few days. This is given into a vein through a central line (intravenous).

The chemotherapy drugs kill off many of the normal bone marrow cells as well as the leukaemia cells. But normal bone marrow cells usually come back after 2 to 3 weeks, and start making blood cells again.

If the patient is not in remission after this treatment, he/she will need more chemotherapy. They may have a different combination of drugs as that from the first time. In recent trials, between 78 to 93% of adults with adult acute lymphoblastic leukaemia got into remission with induction chemotherapy.

The chemotherapy travels through the bloodstream to most parts of the body but does not reach the brain or the testicles. Leukaemic cells can sometimes go into the brain and in men to the testes. So, as part of the remission induction treatment a patient may have chemotherapy given into the fluid that circulates around the spine and brain (called intrathecal chemotherapy). The patient may also have radiotherapy to the brain and spine. If the leukaemia comes back in the testes, the patient will have more chemotherapy or radiotherapy.

Intrathecal chemotherapy means treatment in which anticancer drugs are injected into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord.



[Picture Credit: Intrathecal]

If the patient has Philadelphia positive ALL he/she may have a biological therapy called *imatinib* as well as chemotherapy.

This remission induction phase of treatment destroys nearly all of the leukaemia cells. But a very small number may survive. So, the leukaemia is likely to come back without further treatment. To try to stop this, the patient needs to have the next stage of treatment called consolidation therapy.

<u>Treatment given to stop ALL coming back (consolidation therapy)</u> - once there is no sign of the leukaemia, the patient will need treatment to stop it coming back. Doctors call this consolidation treatment.

It may mean:

- More chemotherapy
- A donor transplant
- A transplant with your own blood stem cells but this is rare

A donor transplant means having high dose chemotherapy followed by bone marrow or stem cells from someone else. The doctor may call this an allogeneic transplant.

A transplant with the patient's own cells is called an autologous stem cell transplant. This is not often used for ALL. Stem cells are collected, then high dose chemotherapy followed by the stem given to the patient through a drip. The patient may have radiotherapy as well.
Bone marrow and stem cell transplants are intensive treatments.

The consolidation treatment the patient has depends on many factors.

These include:

- Whether the lumbar puncture tests find leukaemia cells in the fluid around the brain and spinal cord
- Whether the patient has leukaemia after treatment for a previous cancer
- Whether the leukaemia is completely in remission
- How many times the patient had chemotherapy before the leukaemia went into remission
- The general level of fitness and health of the patient

The doctor will also take into account the patient's wishes and feelings about treatment.

If the leukaemia goes into a complete remission after the induction chemotherapy, the patient may have more chemotherapy. He/she may be able to have a stem cell transplant using the patient's own blood stem cells, but this is not often used.

If a patient had more than one induction chemotherapy course to get into remission, the doctor may suggest a donor transplant, if a donor is available.

A lot of research is looking into the role of transplants in treating adult acute leukaemia. The research is to make these treatments more successful and safer. This is very intensive treatment that can make the patient feel very ill for some time. The patient needs to understand all the risks before it is decided what to do. Unfortunately, sometimes people die due to the treatment, rather than from the leukaemia itself.

Transplants can have long term effects. These are likely to lower the quality of life after finishing treatment. The patient needs to fully understand this before agreeing to any treatment. If the patient has a transplant after remission induction and consolidation, the overall treatment may be shorter and finish in less than a year.

Keeping ALL away long term (maintenance therapy) - the last phase of ALL treatment is maintenance therapy. It helps to keep the leukaemia in remission for longer. It usually involves having low dose chemotherapy and short courses of steroids for up to 2 years. It may also include more treatment to the brain and spine.

Treating ALL that comes back or resists treatment - sometimes, tests find leukaemia cells in the bone marrow after one has had treatment. This is called resistant leukaemia. Such patients may have more chemotherapy, using different drugs as that from the first time. The doctor may also suggest a stem cell transplant, as part of a clinical trial.
If the patient goes into remission, the leukaemia sometimes comes back later on. This is called a relapse.

Treatment for relapsed leukaemia depends on:

- How long the patient was in remission
- The age and general level of fitness and health of the patient
- Certain features of the leukaemia cells

The patient may have the same drugs he/she had when they first went into remission. Or the patient may have a different combination of chemotherapy drugs. The doctor may also suggest a stem cell transplant.

Testicular relapse - for men and boys with ALL, there is a risk that leukaemia cells can spread to the testicles. The treating doctor must be informed immediately upon noticing any swelling or lumps in the testicles.
(Cancer Research UK; Cancer Network).

Side Effects of Treatment
Some people receiving ALL treatment may experience no side effects. Others may face short-term or long-lasting side effects. Among the possible side effects of treatment are:

- anaemia
- infection
- easy bleeding
- nausea and vomiting
- mouth sores
- nerve damage causing pins and needles sensations in the feet and hands
- diarrhoea
- hair loss

There are many ways to manage these side effects. For example, regular hand washing can help lower the risk of infection.
(Harvard Health Publications).

Supportive Care
Since myelosuppression is an anticipated consequence of both leukaemia and its treatment with chemotherapy, patients must be closely monitored during remission induction treatment. Facilities must be available for haematological support and for the treatment of infectious complications.

Supportive care during remission induction treatment should routinely include red blood cell and platelet transfusions, when appropriate.

Evidence (Supportive care):

1. Randomised clinical trials have shown similar outcomes for patients who received prophylactic platelet transfusions at a level of 10 000/mm^3 rather than at a level of 20 000/mm^3.

2. The incidence of platelet alloimmunisation was similar among groups randomly assigned to receive one of the following from random donors:

    - Pooled platelet concentrates.
    - Filtered, pooled platelet concentrates.
    - Ultraviolet B-irradiated, pooled platelet concentrates.
    - Filtered platelets obtained by apheresis.

Empiric broad-spectrum antimicrobial therapy is an absolute necessity for febrile patients who are profoundly neutropaenic. Careful instruction in personal hygiene and dental care and in recognising early signs of infection are appropriate for all patients. Elaborate isolation facilities, including filtered air, sterile food, and gut flora sterilisation, are not routinely indicated but may benefit transplant patients.

Rapid marrow ablation with consequent earlier marrow regeneration decreases morbidity and mortality. White blood cell transfusions can be beneficial in selected patients with aplastic marrow and serious infections that are not responding to antibiotics. Prophylactic oral antibiotics may be appropriate in patients with expected prolonged, profound granulocytopaenia (<100/mm^3 for 2 weeks), though further studies are necessary. Serial surveillance cultures may be helpful in detecting the presence or acquisition of resistant organisms in these patients.

As suggested in a CALGB study (CLB-9111), the use of myeloid growth factors during remission-induction therapy appears to decrease the time to hematopoietic reconstitution. (National Cancer Institute).

Positive Signs of Remission

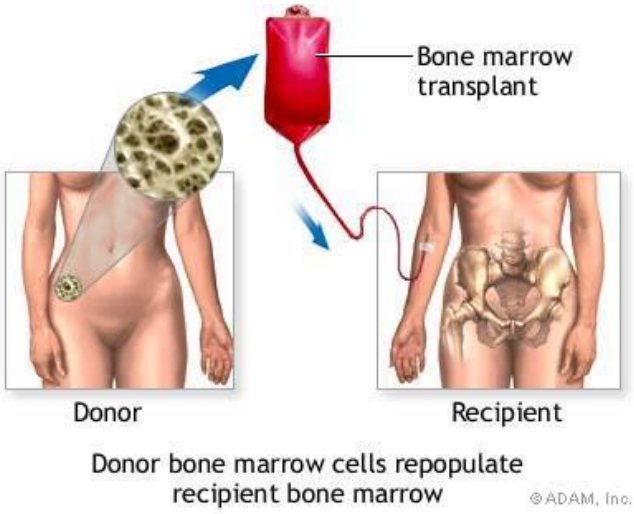
A patient who has received remission-induction treatment of ALL is in remission if all of the following criteria are met:

- Bone marrow is normocellular with no more than 5% blasts
- There are no signs or symptoms of the disease
- There are no signs or symptoms of central nervous system leukaemia or other extramedullary infiltration
- All of the following laboratory values are within normal limits:
    - White blood cell count and differential cell count
    - Haematocrit/haemoglobin level
    - Platelet count

Current approaches to post-remission therapy for adult ALL include short-term, relatively intensive chemotherapy followed by any of the following:

- Longer-term therapy at lower doses (maintenance therapy)
- Allogeneic bone marrow transplant

(National Cancer Institute).



[Picture Credit: Bone Marrow Transplant]

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may

also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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.

Whilst CANSA has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by 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.

Sources and References

American Cancer Society
http://www.cancer.org/cancer/leukemia-acutelymphocyticallinadults/detailedguide/leukemia-acute-lymphocytic-risk-factors

Atom Bomb
http://www.openculture.com/2010/09/how_to_photograph_an_atomic_bomb.html

Blood Cell Development
http://www.cancer.gov/PublishedContent/MediaLinks/711883.html

Bone Marrow Transplant
https://www.google.co.za/search?q=bone+marrow+transplant&source=lnms&tbm=isch&sa=X&ei=rQM0U9CgE9OS7AbYpIDgDA&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=67kFg_2xPLUuPM%253A%3BfOPQFCfuwgFIGM%3Bhttp%253A%252F%252Fwww.x-ald.nl%252Fwp-content%252Fuploads%252F2011%252F08%252Fbone-marrow-transplant.jpg%3Bhttp%253A%252F%252Fwww.x-ald.nl%252Ftreatment-options%252Fhsct%252F%3B400%3B320

Cancer Network
http://www.cancernetwork.com/ash-2014/acute-lymphoblastic-leukemia-responds-immunotherapy

Cancer Research Institute
http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/leukemia

Cancer Research UK
http://www.cancerresearchuk.org/cancer-help/type/all/treatment/which-treatment-for-acute-lymphoblastic-leukaemia
http://www.cancerresearchuk.org/cancer-help/type/all/about/acute-lymphoblastic-leukaemia-risks-and-causes#risks

Center for Environmental Health Studies
http://www.clarku.edu/mtafund/prodlib/jsi/Leukemia_and_Exposure_to_Ionizing_Radiation.pdf

Cleveland Clinic
http://my.clevelandclinic.org/disorders/acute_lymphocytic_leukemia/hic_adult_acute_lymphoblastic_leukemia.aspx

Harvard Health Publications
http://www.drugs.com/health-guide/acute-lymphocytic-leukemia-all-in-adults.html

Identical Twins
https://www.google.co.za/search?q=identical+twins&source=lnms&tbm=isch&sa=X&ei=SQY0U9HcMsqM7AaIlIGIBw&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=666&dpr=0.9#facrc=_&imgdii=_&imgrc=MDjCsClgjuxUBM%253A%3BQmD0MHWSz4oNSM%3Bhttp%253A%252F%252Fwww.paulrichstudio.com%252Fblog%252Fwp-content%252Fuploads%252F2012%252F10%252Fidentical-twins-portland-portrait-photography-

paulrichstudio021.jpg%3Bhttp%253A%252F%252Fwww.paulrichstudio.com%252Fblog%252Felizabeth-isabella-identical-twins%252F%3B900%3B600

Leukaemia and Lymphoma Research
https://leukaemialymphomaresearch.org.uk/information/leukaemia/acute-lymphoblastic-leukaemia-all

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Leukaemiaacutelymphoblastic/AboutALL/Causes.aspx

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/basics/symptoms/con-20042915

MedicineNet.com
http://www.medicinenet.com/script/main/art.asp?articlekey=206196&ecd=mnl_day_081817

Medscape
http://emedicine.medscape.com/article/2004705-overview

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/adultALL/Patient/page1
http://www.meb.uni-bonn.de/Cancernet/CDR0000062864.html
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

NHS Choices
http://www.nhs.uk/Conditions/Leukaemia-acute-lymphoblastic/Pages/Causes.aspx

Obesity
https://www.google.co.za/search?q=obese&source=lnms&tbm=isch&sa=X&ei=5gg0U_3wFcLy7AaTmYDABg&ved=0CAYQ_AUoAQ&biw=1517&bih=666&dpr=0.9#facrc=_&imgdii=_&imgrc=Et1wKe2ljFgCCM%253A%3BOpZ4ILWc9fUD3M%3Bhttp%253A%252F%252Fdigitaljournal.com%252Fimg%252F8%252F3%252F0%252F4%252F6%252F7%252Fi%252F1%252F3%252F3%252Fo%252Fobese_(1).jpg%3Bhttp%253A%252F%252Fdigitaljournal.com%252Farticle%252F338174%3B450%3B295

Oncolink
http://www.oncolink.org/types/article.cfm?c=283&id=9593

University of Maryland Medical Center
http://umm.edu/health/medical/reports/articles/acute-lymphocytic-leukemia

WebMD
http://www.webmd.com/cancer/acute-lymphoblastic-leukemia

Zhang, L., Steinmaus,C., Eastmond, D.A. Xin, X.K. & Smith, M.T. 2008. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Rev. Mutat. Res, doi:10.1016/j.mrrev.2008.07.002.