Cancer Association of South Africa (CANSA)

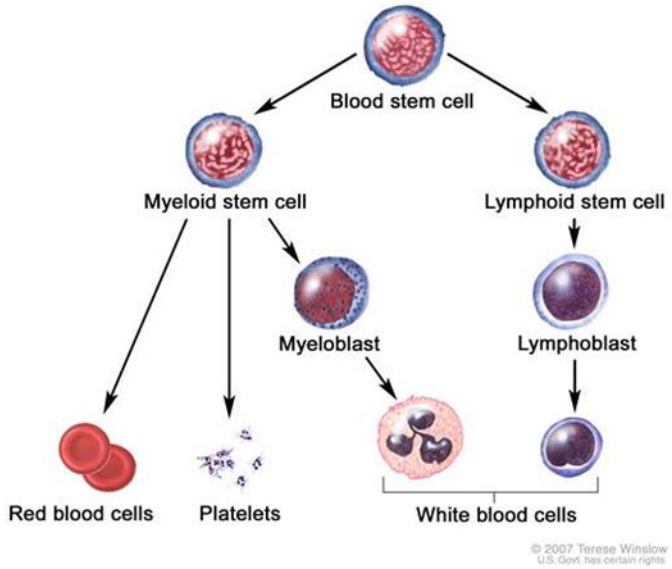
Research • Educate • Support

Fact Sheet on Adult Chronic Myeloid Leukaemia (CML)

Introduction

Blood is made up of blood cells in a liquid called plasma. The blood cells are made in the bone marrow. Bone marrow is a spongy material that is found in the middle of the bones, particularly in the pelvis and backbone (spine). Normally, millions of new blood cells are made every day to replace the old and worn-out blood cells.

[Picture Credit: Blood Cell Formation]



All blood cells are made from cells called stem cells. There are two types of stem cell:

- **lymphoid stem cells**, which make white blood cells called lymphocytes
- **myeloid stem cells**, which make all the other types of blood cells: red blood cells, platelets, and white blood cells called granulocytes.

To begin with, the new blood cells are immature. It does not look like red blood cells, platelets or white blood cells, and they cannot yet perform the functions they are supposed to. These immature cells are called blast cells. Usually, blast cells stay in the bone marrow until they have matured into red blood cells, platelets or white blood cells.

In the bone marrow, the stem cells divide and grow to form fully developed (mature) red blood cells, platelets and white blood cells.

These are then released into the blood to carry out different functions:

- **Red blood cells** contain haemoglobin, which carries oxygen from your lungs to all the cells in your body.
- **Platelets** are very small cells that help blood to clot, and prevent bleeding and bruising.
- **White blood cells** fight and prevent infection. There are several types of white blood cell. The two most important types are neutrophils and lymphocytes.

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Adult Chronic Myeloid Leukaemia (CML)
Chronic Myeloid Leukaemia (CML) usually develops very slowly, which is why it is described as a 'chronic' leukaemia. Many people do not need treatment for months or years. However, some people need to have treatment straight away.

The bone marrow of people with CML make too many of a type of white blood cell called a granulocyte, which is why CML is sometimes called chronic granulocytic leukaemia (CGL). When examined under a microscope, the granulocytes are not fully developed (immature). Over time, these abnormal white blood cells collect in the spleen, causing it to enlarge. They also fill the bone marrow and thereby reducing the number of normal white blood cells, red blood cells and platelets that are manufactured.

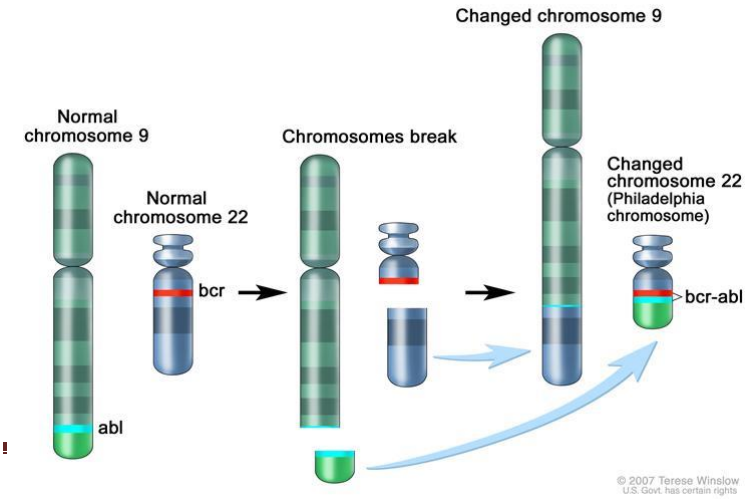
The spleen is an organ on the left side of the abdomen underneath the ribs. It produces small numbers of lymphocytes, stores blood cells, and destroys older, damaged blood cells. It is part of the lymphatic system, which also includes other lymphatic organs such as the bone marrow and the lymph nodes (glands).
(MacMillan Cancer Support).

Chronic myeloid leukaemia (CML) is an uncommon type of cancer of the blood cells. The term "chronic" in chronic myeloid leukaemia indicates that this cancer tends to progress more slowly than acute forms of leukaemia.

Chronic myeloid leukaemia can also be called chronic myelogenous leukaemia and chronic granulocytic leukaemia. The term 'myelogenous' in chronic myelogenous leukaemia refers to the type of cells affected by this cancer. Chronic myelogenous leukaemia typically affects older adults and rarely occurs in children, though it can occur at any age.
(Mayo Clinic).

Chronic myeloid leukaemia (also called CML or chronic myelogenous leukaemia) is a chronic (long-term) disorder of the bone marrow. Bone marrow is the spongy, red tissue that fills the large bones. All of the blood cells are produced in the bone marrow.

People with CML have acquired an abnormality that causes a section of one chromosome (a strand of genes) to break off and attach to another chromosome; this results in an abnormally short chromosome, known as the Philadelphia chromosome. This exchange of genetic information causes two genes, BCR and ABL, to fuse into one gene, called BCR-ABL.



The BCR-ABL gene causes bone marrow cells to produce an abnormal enzyme (the BCR-ABL tyrosine kinase); this enzyme stimulates white blood cells to grow out of control, resulting in elevations of the white blood cell count and an increase in the size of the spleen. Eventually, the disease can transform into a more aggressive disease, called acute leukaemia.

[Picture Credit: BCR-ABL Gene]

People with acute leukaemia have an increased number of immature white blood cells (called blast cells). The overgrowth of blast cells leads to an inadequate number of mature white blood cells, which limits production of other vital blood cells, including red blood cells and platelets. Having a decreased number of blood cells and platelets can increase the risk of developing infections or bleeding excessively.
(Uptodate).

Incidence of Adult Chronic Myeloid Leukaemia (CML)

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.

Causes of Adult Chronic Myeloid Leukaemia (CML)
Chronic myeloid leukaemia occurs when something goes awry in the genes of your blood cells. It's not clear what initially sets off this process, but doctors have discovered how it progresses into chronic myeloid leukaemia.

First, an abnormal chromosome develops - human cells normally contain 23 pairs of chromosomes. These chromosomes hold the DNA that contains the instructions (genes) that control the cells in your body. In people with chronic myeloid leukaemia, the chromosomes in the blood cells swap sections with each other. A section of chromosome 9 switches places with a section of chromosome 22, creating an extra-short chromosome 22 and an extra-long chromosome 9.

The extra-short chromosome 22 is called the Philadelphia chromosome, named for the city where it was discovered. The Philadelphia chromosome is present in the blood cells of 90 percent of people with chronic myeloid leukaemia.

Second, the abnormal chromosome creates a new gene - the Philadelphia chromosome creates a new gene. Genes from chromosome 9 combine with genes from chromosome 22 to create a new gene called BCR-ABL. The BCR-ABL gene contains instructions that tell the abnormal blood cell to produce too much of a protein called tyrosine kinase. Tyrosine kinase promotes cancer by allowing certain blood cells to grow out of control.

Third, the new gene allows too many diseased blood cells - the blood cells originate in the bone marrow, a spongy material inside the bones. When the bone marrow functions normally, it produces immature cells (blood stem cells) in a controlled way. These cells then mature and specialise into the various types of blood cells that circulate in the body — red cells, white cells and platelets.

In chronic myeloid leukaemia, this process does not work properly. The tyrosine kinase caused by the BCR-ABL gene causes too many white blood cells. Most or all of these contain the abnormal Philadelphia chromosome. The diseased white blood cells do not grow and die like normal cells. The diseased white blood cells build up in huge numbers, crowding out healthy blood cells and damaging the bone marrow.
(Mayo Clinic).

Phases of Adult Chronic Myeloid Leukaemia
There are three phases of CML:

Chronic phase - in the chronic phase, there are less than 5 percent immature blast cells in the bone marrow. Approximately 85 percent of people are in the chronic phase when they are initially diagnosed. This phase generally lasts several years and is readily controlled with oral medications.

Accelerated phase - during the accelerated phase, maturation of white blood cells becomes progressively impaired, and there are between 10 and 19 percent blast cells in the blood or bone marrow. The number of abnormal cells in the body is more difficult to control with medications, likely because of new mutations that develop in the blast cells.

Blast phase - in blast crisis (blast phase), there are more than 20 to 30 percent blast cells in the blood or bone marrow. Before recent advances in treatment, blast crisis typically

occurred within four to five years after diagnosis and was often unresponsive to treatment. (Uptodate).

Signs and Symptoms of Adult Chronic Myeloid Leukaemia
The following are signs and symptoms of Adult Chronic Myeloid Leukaemia:

Getting infections more often than usual - due to a shortage of healthy white blood cells to fight off infections, the infections may happen more often, may be more severe and may take longer to clear than usual.

Weight loss - CML can use up energy that the body would otherwise use or store. So one may lose weight, even if eating normally. If someone has a very enlarged spleen, he/she may feel full more quickly than usual because the spleen is causing pressure on the stomach. This may make the patient eat less and lose weight.

Tiredness and looking pale - it is common for people with CML to feel very tired. This is because your bone marrow isn't able to make enough red blood cells. They are crowded out by the large numbers of abnormal white blood cells. A shortage of red blood cells is called anaemia. This can make you feel breathless and tired.

Swollen lymph glands - abnormal white blood cells collecting in the lymph glands may cause swelling.

Abnormal bruising or bleeding - low levels of platelets in the blood can cause bleeding or bruising. You may find that you bruise more easily than usual or with no obvious cause. You may also have bleeding from the gums or nose. More rarely people notice a fine rash of dark red spots (called purpura). Some people also have blood in their urine or stools.

Abdominal discomfort - the spleen is an organ on the left side of your body, just under your ribs. In CML it can become swollen and larger than normal. This can cause discomfort or pain in your tummy (abdomen). Your doctor may be able to feel your enlarged spleen.

A poor appetite - some people find that they gradually lose their appetite. It can be due to the swollen spleen pressing on the stomach.

Sweating at night - some people have sudden onsets of a high temperature (fever) and sweating. This can occur more often at night.

Headaches - if you have a very high white blood cell count, the extra cells can clog the smallest blood vessels in the brain. This can cause headaches in some people.

Bone pain - sometimes people with chronic leukaemia get aches in their bones. This is because there are leukaemia cells building up in the bone marrow, increasing pressure on nerves and causing pain.

Strokes - in some patients with chronic myeloid their bone marrow may make too many platelets and they can develop abnormal blood clotting, which can cause strokes.

Less common symptoms include:

These symptoms may also occur but are usually in the later stages of CML.
Eyesight changes - if you have a very high white blood cell count, the extra cells can clog the smallest blood vessels in the eyes. This can cause eye problems in some people with chronic myeloid leukaemia.

Swollen, painful joints - some people get swollen joints due to a build up of body salts in the tissues.

Persistent painful erection - doctors call this priapism. It is a rare symptom that can happen in men with CML. Priapism is an erection that won't go down and can become very painful. It is caused by the abnormally high number of white blood cells in the blood blocking up tiny blood vessels in the penis. A priapism is an emergency. If you have persistent painful erection then you need medical attention. An erection that lasts too long can cause permanent damage to the penis.

Changes in kidney function - some people with advanced stages of CML have damage to their kidneys.
(Cancer Research UK; Medicine.Net).

Complications of Adult Chronic Myeloid Leukaemia (CML)
Chronic myelogenous leukaemia (CML) can cause a variety of complications, including:

Fatigue - if diseased white blood cells crowd out healthy red blood cells, anaemia may result. Anaemia can make one feel tired and worn down. Treatment for CML also can cause a drop in red blood cells.

Excess bleeding - blood cells called platelets help control bleeding by plugging small leaks in blood vessels and helping the blood to clot. A shortage of blood platelets (thrombocytopaenia) can result in easy bleeding and bruising, including frequent or severe nosebleeds, bleeding from the gums, or tiny red dots caused by bleeding into the skin (petechiae).

Pain - CML can cause bone pain or joint pain as the bone marrow expands when excess white blood cells build up.

Enlarged spleen - some of the extra blood cells produced when one has CML are stored in the spleen. This can cause the spleen to become swollen or enlarged. The swollen spleen takes up space in the abdomen and makes one feel full even after small meals or causes pain on the left side of the body below the ribs.

Infection - white blood cells help the body fight off infection. Although people with CML have too many white blood cells, these cells are often diseased and do not function properly. As a result, they are not able to fight infection as well as healthy white cells can. In addition, treatment can cause the white cell count to drop too low (neutropaenia), also making one vulnerable to infection.

Death -if CML cannot be successfully treated, it ultimately is fatal.
(Mayo Clinic).

Staging in Adult Chronic Myeloid Leukaemia (CML)
In most forms of cancer some form of staging is used to assist in treatment planning and in making a likely prognosis. In solid tumours, staging refers primarily to the spread of the cancer from its original site. However this form of staging is not used in CML because the disease is typically widespread at the time of diagnosis.

Most patients are diagnosed in chronic phase and when they are treated with imatinib they will usually remain in this phase for a long period. When blast crisis occurs, it is characterised by the presence of at least 30% blast cells in the bone marrow or circulating blood. About half of all blast crises are of the myeloid type, a quarter are of the lymphoid type and the remainder are a mixture of the two. The distinction is important because it can predict the likely response to treatment and eventual outcome (prognosis). Some patients will develop localised collections of leukaemia cells outside the bone marrow. Although this is uncommon, it is usually followed by typical blast crisis within a few months.

The Sokal and Hasford scores have been devised to help doctors predict which patients are more likely to have progressive disease. The scores separate patients into good and poor-risk groups using formulas based on the following features:

- patient's age
- size of spleen
- percentage of blast cells in the blood
- number of platelets
- numbers of basophils
- numbers of eosinophils.

Before the introduction of imatinib, patients with low scores had an average survival of around eight years whilst patients with high scores had an average survival of three to four years.

The use of imatinib is expected to greatly extend these survival periods but the evidence to date suggests that the two scoring systems can still be useful for patients. However, it is too early to accurately assess the average survival for the good and poor-risk groups. New techniques to predict the response to treatment are being developed and will eventually replace these older scoring systems.
(Leukaemia & Lymphoma Research).

Treatment of Adult Chronic Myeloid Leukaemia (CML)
Treatment decisions for people with chronic myeloid leukaemia (CML) are complex due to the variety of available options. Currently, the most frequently used treatment options include:

- Disease control with oral tyrosine kinase inhibitors (TKIs) such as imatinib (brand name: Gleevec), dasatinib (brand name: Sprycel), or nilotinib (brand name: Tasigna)
- Potential cure with haematopoietic cell transplantation (also called bone marrow transplantation), usually after the disease stops responding or relapses during treatment with a TKI
- Treatment to reduce symptoms with chemotherapy (hydroxyurea, busulfan, or interferon alpha with or without cytarabine)

The choice of therapy depends upon the phase of CML, the availability of a stem cell donor, the patient's candidacy for stem cell transplantation, and the patient's preference.

Response to treatment - the primary goal of treatment is to reduce or eliminate the cells with the abnormal Philadelphia chromosome. This is measured as the cytogenetic response. Such treatment, if effective, will also return the blood counts to normal. This is measured as the haematologic response.

While achieving a hematologic response will reduce the severity of symptoms associated with CML, progression to the accelerated or blast phase will continue unless a cytogenetic response is achieved. Achieving a hematologic response is important, but does not ensure that the disease is adequately controlled.
Another way to determine how well the disease is controlled is to perform sensitive molecular testing. A person is said to have a complete molecular response when there is no evidence of the BCR-ABL gene. The goal of hematopoietic cell transplantation is to achieve this level of response. A molecular response is sometimes seen during longer term follow up of people treated with TKIs. Chemotherapy rarely, if ever, produces such a response.

Tyrosine Kinase Inhibitors (TKIs)
The Philadelphia chromosome, characteristic of chronic myeloid leukaemia (CML), gives rise to the formation of a unique gene product, an abnormal enzyme called the BCR-ABL tyrosine kinase. Researchers directed their efforts at developing compounds that could selectively inhibit this abnormal enzyme, resulting in the development of a class of medications known as tyrosine kinase inhibitors (TKIs). TKIs slow or stop the actions of BCR-ABL, which leads to the rapid death of cells containing the abnormal Philadelphia chromosome. Normal cells suffer fewer toxic effects from TKIs compared with traditional chemotherapy treatments.

Although they have not been proven to cure the disease, TKIs are able to achieve long-term control of CML in the majority of people; thus, they have become the initial treatment of choice for almost all people who are newly diagnosed with CML. All of the available TKIs are able to induce hematologic and cytogenetic responses in all stages of the disease [1-3]. As a result, a choice among these medications is usually based upon the patient's medical history and the potential side effects of each medication).

Many prescription and non-prescription medications can interact with TKIs, potentially making the treatment less effective or dangerously increasing the amount of drug in the bloodstream. Two non-prescription medications that should be avoided are acetaminophen (brand name: Tylenol) and St. John's wort (also called hypericum perforatum). Grapefruit juice should also be avoided.

Imatinib (brand name: Gleevec) - Imatinib mesylate is a TKI that can be used in people with all phases of CML. It is proven to have significant benefits. One study comparing imatinib versus interferon plus cytarabine (a form of chemotherapy) for people with newly diagnosed, chronic phase CML found that 97 percent of people who were given imatinib had a complete hematologic response rate, and 76 percent achieved a complete cytogenetic response.

Further follow-up is needed to determine how long responses will last, although the relapse rate has been remarkably low in people followed for seven or more years who achieved a

complete cytogenetic response. At present, experts recommend continuing imatinib treatment indefinitely because the disease recurs, often within months, in the majority of people who stop taking it. Progression to blast crisis can occur despite imatinib treatment in people with accelerated phase disease and in those who acquire new genetic mutations.

The medication should be taken by mouth once daily, with a meal and a large glass of water. It is extremely important to take every single scheduled dose of your imatinib. Skipping pills can seriously jeopardize your chances of having a good response. One study showed that you need to take over 90 percent of your pills to have a chance of a sustained complete response.

Side effects - Imatinib is generally very well tolerated; most side effects are mild to moderate and do not cause the person to stop taking it. Less than 5 percent of people will be unable to tolerate long-term treatment with imatinib.

Common side effects include:

- Nausea and vomiting, although this is not usually a problem when the drug is taken with meals.
- Diarrhoea is usually mild to moderate, but can be severe. It generally responds to treatment with loperamide (brand name: Imodium).
- Muscle cramps are perhaps the most bothersome long-term symptom associated with imatinib, most commonly affecting the calves, feet, and hands. There is no definitive treatment, although some people benefit from treatment with calcium or magnesium supplements.
- Skin rash is uncommon. When it occurs, it is usually mild and often resolves with continued treatment.
- Breast enlargement (gynaecomastia) may occur in a small number of men.
- Mild anaemia, which manifests as fatigue or listlessness, is not uncommon in people who use imatinib for long periods.
- Some patients note mild to moderate fatigue.

Pregnancy - Women and men who take imatinib usually have no increased difficulty achieving pregnancy. However, the risk of miscarriage and birth defects while taking imatinib is uncertain. Thus, men and women who take imatinib are strongly advised to use a birth control method during treatment.

Women who take imatinib and become pregnant are left with a difficult choice:

- Continuing imatinib may result in damage to the developing foetus.
- Stopping imatinib may allow CML to relapse in the mother.

In one series of women exposed to imatinib during pregnancy, 50 percent delivered a healthy baby, 28 percent elected to have a termination, 14 percent had a miscarriage, and approximately 10 percent had a baby with a birth defect. In addition, imatinib is passed into breast milk, and breastfeeding women are advised to avoid imatinib. Women who become pregnant while taking imatinib should speak with their healthcare provider as soon as possible.

Dasatinib (brand name: Sprycel) - Dasatinib is a second generation TKI that may be recommended for treatment of CML after imatinib. It can also be used as initial treatment instead of imatinib. It is taken by mouth once or twice daily.

Side effects - Up to 35 percent of people who take dasatinib for advanced phase CML can develop a pleural effusion, a collection of fluid in space between the lining of the lung (the pleura) and the chest wall. In some cases, this complication requires a reduction in the dose of dasatinib, a temporary break in treatment, or a procedure to drain the fluid. Pleural effusions occur in approximately 10 percent of patients treated with dasatinib in chronic phase and generally tend to be of less clinical severity than in patients with advanced CML.

Rarely, patients have developed pulmonary hypertension-high blood pressure in the blood vessels that carry blood to the lungs. Pulmonary hypertension causes people to have trouble breathing and to feel very tired.

Women who are pregnant or breastfeeding should not use dasatinib due to the potential risk of harm to the infant; men and women are strongly encouraged to use a birth control method during treatment.

Nilotinib (brand name: Tasigna) - Nilotinib is another second generation TKI that may be recommended for treatment of CML after imatinib. It can also be used as initial treatment instead of imatinib. It should be taken by mouth on an empty stomach (one hour before or two hours after eating) every 12 hours; taking the medication with food can lead to excessive amounts of the drug in the bloodstream and is not recommended.

Side effects - The most common side effects of nilotinib include rash, itching, nausea, and constipation. An abnormal heart rhythm, known as QT prolongation, is a potential side effect of both dasatinib and nilotinib. QT prolongation can potentially cause sudden cardiac death, although this complication is very rare. People who have an electrolyte imbalance (low blood level of potassium or magnesium), an abnormal heart rhythm, or who take medication to regulate their heart rhythm should talk with their doctor about the need for additional monitoring while taking dasatinib or nilotinib.

There is a higher rate of cardiovascular complications in patients receiving nilotinib compared with those receiving imatinib, particularly in individuals with cardiovascular risk factors (high blood pressure, high blood cholesterol, diabetes, smokers). These complications include stroke, heart attacks, and symptoms related to decreased blood flow to the legs. The latter is called "peripheral artery disease" and can cause leg pain that gets worse with activity. Muscle pain that gets worse with activity and improves with rest is called ‘claudication’.

Women who are pregnant or breastfeeding should not use nilotinib; men and women are strongly encouraged to use a birth control method during treatment.

Bosutinib (brand name: Bosulif) - Bosutinib is another TKI that may be recommended for treatment of CML after failure of another TKI. It should be taken daily by mouth with food. Major side effects include diarrhoea, abnormalities in liver function tests, and nausea and vomiting. Some patients have fluid retention. Fluid retention includes swelling in the legs (called oedema) and fluid around the lungs (called pleural effusion). Women who are pregnant or breastfeeding should not use bosutinib; men and women are strongly encouraged to use a birth control method during treatment.

Ponatinib (brand name: Iclusig) - Ponatinib is another TKI that may be recommended for treatment of CML that has relapsed or is unresponsive to treatment with other TKIs. It is the only TKI that is active in CML with certain mutations (eg, T315I). Due to concerns regarding dangerous side effects, ponatinib is reserved for use in patients who are not candidates for other TKIs. Potentially life-threatening side effects include cardiovascular problems (stroke, heart attack, peripheral artery disease), inflammation of the pancreas (pancreatitis), and liver failure. Women who are pregnant or breastfeeding should not use ponatinib; men and women are strongly encouraged to use a birth control method during treatment.

If the tyrosine kinase inhibitor fails - People who cannot tolerate, fail to respond, or stop responding to an initial TKI are faced with the decision of what treatment to try next. The options include:

- Control the disease with another TKI, and then proceed as soon as possible with hematopoietic cell transplantation.
- Control the disease with another TKI with plans to proceed with transplantation if the disease relapses a second time.
- If the disease relapses despite treatment with another TKI and transplantation is not an option, treatment with interferon alpha can help to reduce symptoms and prolong survival.
- Relapses during treatment with a TKI are often due to the development of a new mutation in the BCR-ABL gene, which allows the disease to become resistant to treatment. Testing to determine whether additional mutations have developed in the BCR-ABL gene (called mutation analysis) can be performed. Some mutations (eg, T315I) will not respond to commonly available tyrosine kinase inhibitors (imatinib, dasatinib, or nilotinib); people with these mutations are generally encouraged to consider transplantation.

If transplantation is not an option, options include treatment with omacetaxine (brand name: Synribo), ponatinib, or enrollment on a clinical trial. Omacetaxine is a chemotherapy that can be given as an injection under the skin daily for two weeks and repeated every four weeks for a maximum of six cycles. Side effects include infection, diarrhoea, nausea, fever, and fatigue.

A major cause of treatment ‘failure’ is poor compliance with taking the medication, meaning the patient has been skipping doses or not taking the medication as directed. Therefore, it is critical that the doctor be certain that the patient was actually taking the TKI treatment before switching therapies.

Immunotherapy - Immunotherapy is not necessarily the first treatment choice for chronic myeloid leukaemia (CML). This is because targeted therapy with medicines works so well for CML.

The treatment may be used if your CML is in the chronic phase and is not responding to targeted medicines. Immunotherapy may then be done with a medicine called interferon alpha. This medicine may kill leukaemia cells or help keep them under control. The goal is to destroy as many leukaemia cells as possible.

The treatment is not as useful for CML in the accelerated or blast phase. When it is used, remission doesn't last as long. Remission is when there are no more signs of the disease.
(University of Rochester Medical Center).

Haematopoietic Cell Transplantation

In hematopoietic cell transplantation, also referred to as bone marrow transplantation or stem cell transplantation, the patient's diseased bone marrow (hematopoietic) cells are replaced with healthy ones from a donor.

Choice of donor - The donor is a person other than the patient; this is called an **allogeneic transplant**. Allogeneic transplants can come from a relative (e.g., sibling) or from an unrelated donor. Within a family, the best chance for a match comes from siblings who have the same parents as the patient. Each sibling has a one in four chance of matching an individual patient. Since many people do not have a sibling who matches, unrelated donors may be used. Related or unrelated donors who are fully HLA-matched are preferred. Under some circumstances, partially or half-matched (haploidentical) donors can be used.

In chronic myeloid leukaemia (CML), the chances of success with haematopoietic cell transplantation are directly related to the phase of disease at the time of the transplant. In the past, transplantation of people in chronic phase within the first year resulted in the best outcomes.

Several studies have suggested that treatment with a tyrosine kinase inhibitor (TKI) prior to transplantation does not reduce the chance that transplantation will be successful, although additional studies are needed to confirm this finding.

If a matched sibling donor can be found, 50 to 85 percent of people with CML transplanted in the first or second chronic phase of their disease achieve long-term remissions. Disease-free survival falls to 30 to 40 percent in people transplanted in the accelerated phase, and to 10 to 20 percent in people transplanted in blast phase.

A patient's age has a major influence on the outcome after transplantation with cells from a sibling donor. In the subgroup of people under age 50 who undergo this procedure during the first year of diagnosis, 70 to 85 percent will be alive and free of disease five years later. However, people up to 60 years of age have successfully undergone allogeneic transplantation with treatments that completely destroy the bone marrow (myeloablative treatment). The development of reduced intensity regimens, which have reduced toxicity, has permitted even older people to be successfully transplanted.

Relapse after transplant - Relapse or recurrence of CML may occur if cells containing the Philadelphia chromosome remain after the transplant procedure. However, finding residual disease with sensitive molecular tests in the first six months following transplantation is **not** associated with eventual relapse because the anti-tumour effects of the graft may eventually prevail.

Relapse can be treated with a TKI or with infusions of leukocytes from the original donor, with the hope of mounting a more effective graft-versus-tumour effect. Donor leukocyte infusions (DLIs) can be extremely effective, and remissions attained after DLI appear to be

quite durable. However, graft-versus-host disease, and in some instances graft failure, may complicate DLI
(UpToDate).

Prognosis (Outlook)
With ten years' experience of using imatinib to treat CML, there is a general agreement that this drug will prevent progression of disease in the majority of patients. The use of imatinib and other drugs has also led to a very significant improvement in survival and in quality of life.

For patients who do not achieve a good response to imatinib or nilotinib, the outlook will depend on their response to alternative treatments. They will need to discuss treatment options and likely prognosis with their specialist.

The minority of patients who are diagnosed in blast crisis, on the other hand, have gained much less benefit from the introduction of imatinib and related drugs. Such patients may well benefit by taking part in a clinical trial.
(Leukaemia & Lymphoma Research).

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).

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Blood Cell Formation
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