

Cancer Association of South Africa (CANSA)



Fact Sheet on Adult Chronic Myeloid Leukaemia (CML)

Introduction

Blood is made up of blood cells and 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.

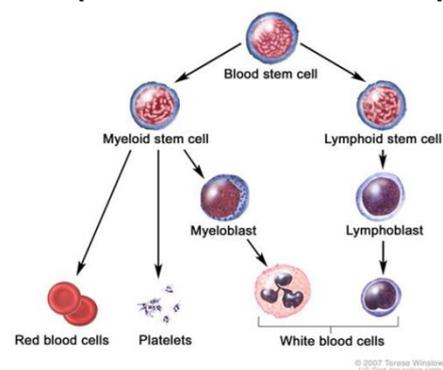


All blood cells are made from cells called stem cells. There are two types of stem cell:

- **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.

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

[Picture Credit: Blood Cell Formation]



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 immediately.

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; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

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March 2019

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). 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.

Flis, S. & Chonjnacki, T. 2019.

“Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of hematopoietic stem cells. At the molecular level, the disorder results from t(9;22)(q34;q11) reciprocal translocation between chromosomes, which leads to the formation of an oncogenic *BCR-ABL* gene fusion. Instead of progress in the understanding of the molecular etiology of CML and the development of novel therapeutic strategies, clinicians still face many challenges in the effective treatment of patients.”

Incidence of Adult Chronic Myeloid Leukaemia (CML)

In providing the incidence figures of Leukaemia in South Africa, The National Cancer Registry (2014) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the ‘Frequency of Histologically Diagnosed Cancer in South Africa’ Section of the Registry .

According to the National Cancer Registry (2014) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2014:

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	366	1:598	1,99%
Asian males	8	1:1 041	0,99%
Black males	163	1:1 264	1,47%
Coloured males	54	1:313	1,29%
White males	140	1:225	0,68%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	258	1:1 069	0,68%
Asian females	12	1:1 607	1,04%
Black females	118	1:2 104	0,73%
Coloured females	36	1:684	0,88%
White females	91	1:363	0,56%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	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	81	28	30	46	48	74	39	17
Asian males	1	1	1	1	0	3	1	0
Black males	49	18	19	25	18	20	5	2
Coloured males	12	4	3	5	9	10	8	2
White males	12	5	6	18	18	23	30	11

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Group - Females 2014	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	54	30	24	36	37	40	26	10
Asian females	2	1	0	4	0	4	0	0
Black females	28	22	14	19	16	10	4	2
Coloured females	10	2	3	2	5	8	2	3
White females	12	5	5	10	16	16	20	5

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 one's blood cells. It is not clear what initially sets off this process, but doctors have discovered how it progresses into chronic myeloid leukaemia.

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. 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.

Signs and Symptoms of Adult Chronic Myeloid Leukaemia

The following are signs and symptoms usually seen in 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 without trying to lose weight - 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.

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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.

Complications of Adult Chronic Myeloid Leukaemia (CML)

Chronic myeloid leukaemia (CML) may cause 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 (thrombocytopenia) 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.

Caocci, G., Mulas, O., Abruzzese, E., Luciano, L., Iurlo, A., Attolico, I., Castagnetti, F., Galimberti, S., Sgherza, N., Bonifacio, M., Annunziata, M., Gozzini, A., Orlandi, E.M., Stagno, F., Binotto, G., Pregno, P., Fozza, C., Trawinska, M.M., De Gregorio, F., Cattaneo, D., Albano, F., Gugliotta, G., Baratè, C., Scaffidi, L., Elena, C., Pirillo, F., Scalzulli, E., La Nasa, G., Foà, R. & Breccia, M. 2019. “Arterial occlusive events (AOEs) represent emerging complications in chronic myeloid leukemia (CML) patients treated with ponatinib. We identified 85 consecutive CML adult patients who were treated with ponatinib in 17 Italian centers. Patients were stratified according to the Systematic Coronary Risk Evaluation (SCORE) assessment, based on sex, age, smoking habits, systolic blood pressure, and total cholesterol levels. The 60-month cumulative incidence rate of AOEs excluding hypertension was 25.7%. Hypertension was reported in 14.1% of patients. The median time of exposure to ponatinib was 28 months (range, 3-69 months). Patients with a high to very high SCORE risk showed a significantly higher incidence rate of AOEs (74.3% vs. 15.2%, $p < 0.001$). Patients aged ≥ 60 years showed a significantly higher incidence rate of AOEs (51.5% vs. 16.9%, $p = 0.008$). In multivariate analysis, no association was found between AOEs and positive history of CV disease, age, dose of ponatinib, previous exposure to nilotinib, and comorbidities. Only the SCORE risk was confirmed as a significant predictive factor ($p = 0.01$; HR=10.9; 95% C.I.=1.7-67.8). Patients aged ≥ 60 years who were treated with aspirin had a lower incidence rate of AOEs (33.3% vs. 61.8%). Among the 14 reported AOEs, 78.6% of them showed grade 3-4 toxicity. This real-life study confirmed the increased incidence of AOEs in CML patients treated with ponatinib, with high to very high SCORE risk. We suggest that patients aged ≥ 60 years who were treated with ponatinib should undergo prophylaxis with 100 mg/day of aspirin. Our findings emphasize a personalized prevention strategies based on CV risk factors.”

Sasaki, K., Kantarjian, H.M., O'Brien, S., Ravandi, F., Konopleva, M., Borthakur, G., Garcia-Manero, G., Wierda, W.G., Daver, N., Ferrajoli, A., Takahashi, K., Jain, P., Rios, M.B., Pierce, S.A., Jabbour, E.J. & Cortes, J.E. 2019.

“Patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs) have near-normal life expectancies. With this comes the possibility of developing second cancers; we aimed to evaluate the incidence of second malignancies in patients with CML using Surveillance, Epidemiology, and End Results Program data. We identified 13,276 patients with CML newly diagnosed in 2001-2014. Patients who had prior history of cancer, a concurrent diagnosis of other malignancies in the same diagnostic year, or a second leukemia after CML diagnosis were excluded. Second malignancies were observed in 597 patients (4%) with a median follow-up of 69 months. The 5- and 10-year cumulative incidences of death for all patients were 30.5% and 41.8%. The 5- and 10-year cumulative incidences of second malignancies were 4.4% and 7.2%, respectively. The overall standardized incidence ratio (SIR) was 1.204. Increased SIRs compared to the general population were observed for the male genital system, 1.593; digestive system, 1.291; skin, 1.588; and urinary system, 1.366. Overall excess absolute risk was 1.714 per 1000 person-years at risk. Our results suggest that relative incidence of overall second malignancies in CML is slightly higher than that of the general population, with minimal increase in the excess absolute risk.”

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.

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.

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 may include:

- Disease control with oral medication
- Potential cure with bone marrow transplantation
- Treatment to reduce symptoms with chemotherapy

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.

Fachi, M.M., Tonin, F.S., Leonart, L.P., Rotta, I., Fernandez-Llimos, F. & Pontarolo, R. 2019.

AIMS: Despite their overall favourable safety profile, tyrosine kinase inhibitors (TKIs) are related to severe adverse events (AEs) including haematological toxicities such as anaemia, leukopenia, neutropenia, and thrombocytopenia. We designed a systematic review and network meta-analysis of randomised controlled trials (RCT) to compare safety among TKIs (bosutinib, dasatinib, imatinib, nilotinib, ponatinib, and radotinib) used by patients diagnosed with chronic myeloid leukemia (CML).

METHODS: We obtained data from the PubMed, Scopus, Web of Science, and SciELO databases. The Bayesian approach was used for direct and indirect comparisons, and the treatments were ranked by the surface under the cumulative ranking curve (SUCRA).

RESULTS: Seventeen studies were included in the network meta-analysis. Our data shows that dasatinib was generally considered worse than the other TKIs, with SUCRA values for 140 mg dasatinib of 90.3% for anaemia, 87.4% for leukopenia, 90.6% for neutropenia, and 97.2% for thrombocytopenia. In addition, nilotinib was shown to be safer, with SUCRA values for 600 and 800 mg doses of 21.9 and 35.8% for anaemia, 23.8 and 14.6% for leukopenia, 33.0 and 17.7% for neutropenia, and 28.7 and 32.6% for thrombocytopenia, respectively.

CONCLUSION: Dasatinib appeared as the least safe drug for CML, most likely because it binds to multiple key kinase targets, being more prone to cause serious haematological AEs. Nilotinib demonstrated a safer profile, mostly due to its selective binding capacity.

Lee, H.R. & Baek, K.H. 2019.

“The majority of natural killer (NK) cells serve an important role in eliminating malignant cells. The cytotoxic effects of NK cells were first identified against leukemia cells, and it is now hypothesized that they may have a critical role in leukemia therapy. The cellular functions of NK cells are mediated by their cell surface receptors, which recognize ligands on cancer cells. The role of NK cells is specifically regulated by the activating or inhibitory killer cell immunoglobulin-like receptors (KIRs) on their surface, which bind to the human leukocyte antigen (HLA) class I ligands present on the target cells. The association between KIR and HLA is derived from the diversity of KIR/HLA gene profiles present in different individuals, and this determines the cytotoxic effect of NK cells on cancer cells. Chronic myeloid leukemia (CML) is a hematological leukemia characterized by the hyper-proliferation of myeloid cells, with the majority of patients with CML presenting with abnormal immune cells. Tyrosine kinase inhibitors are the present standard therapy for CML, but are associated with numerous adverse side effects. Various studies have proposed CML therapy by immunotherapeutic approaches targeting the immune cells. This review summarizes the contents of NK cells and the association between KIR/HLA and leukemia, especially CML. This is followed by a discussion on the development of NK cell immunotherapy in hematological malignancies and research into strategies to enhance NK cell function for CML treatment.”

Chan, O., Talati, C., Sweet, K. & Pinilla-Ibarz, J. 2019.

“Chronic myeloid leukemia (CML) has long been thought to be the model disease for immunotherapy with its characteristic BCR-ABL fusion protein. Although targeted therapy using tyrosine kinase inhibitors (TKIs) is highly effective at inducing remission, most patients require life-long TKI to decrease the risk of relapse. In recent years, much effort has been devoted to finding ways to eliminate CML stem cells (LSCs); the source of disease persistence. Areas covered: In this review, the authors present recent immunologic findings pertinent to CML, vaccinations targeting leukemia antigens, interferon combination therapies, and other emerging strategies aimed at increasing immunogenicity and improving outcomes in patients with CML. Recent publications and abstracts found in Pubmed and hematology/oncology meetings related to these topics were identified and incorporated into this review. Expert commentary: Further understanding of the immune system and antigenic composition of LSCs has allowed for novel therapeutic development. Immunotherapies are effective at the malignant stem cell level and combining these approaches with TKI is a promising option. Despite ongoing challenges, it is increasingly recognized that a cure may be achievable through immunotherapies.”

Aladağ, E. & Haznedaroğlu, İ.C. 2019. Current perspectives for the treatment of chronic myeloid leukemia.

“With an annual incidence of 1-2 in a million, Ph*(+) chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disease that makes myeloid neoplastic cells breed out of control. This BCR-ABL(+) myeloproliferative disease makes up about 15%-20% of all leukemia cases in adults. CML is seen more in males than females, with a rate of three to two. However, it does not show differences in prevalence in terms of age. CML consists of three clinical phases. The first one is the chronic phase, defined by rising white blood cell levels and also by myeloid proliferation and bone marrow maturation. While this phase does not exhibit complications, in diagnosis, it comprises most of the patients. The second phase is the accelerated phase, which the disease progresses to if it is not treated or does not respond to treatment. This usually takes about 3 years. The third phase is the blastic phase. The chronic phase can still progress to the next two phases within the first 2 years, with a rate of 10%. In the following years, the possibility increases by 15%-20% each year. Tyrosine kinase inhibitors (TKIs) are revolutionary drugs for the management of disease course in CML. The aim of this review is to assess current approaches to CML patients' follow-up and treatment with

TKIs. A literature search on CML and TKIs was made in PubMed, Web of Science, and Scopus with particular focus on randomized clinical trials, recommendations, guidelines, and expert opinions. In managing CML, various treatment methods have been utilized for many decades. Prior to the development of TKIs, interferon alpha was the primary tool, which was then complemented by allogeneic hematopoietic stem cell transplantation (HSCT). HSCT was successful in slowing the disease down in the long term and curing up to 50% of patients. Then the coming of the imatinib era opened up different treatment perspectives. For the patients resistant or intolerant to imatinib, second- and third-generation TKIs are successfully used in distinct CML disease states. The survival benefits of TKIs including imatinib, nilotinib, dasatinib, bosutinib, and ponatinib for CML patients are outstanding. TKI-related adverse events could impact the clinical course, especially in long-term drug administrations. The current aim for CML disease management in the TKI era is to provide age- and sex-matched normal life duration to CML patients.”

About Clinical Trials

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

Clinical trials include:

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

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

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

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Blood Cell Formation

https://www.google.co.za/search?q=adult+chronic+myeloid+leukaemia&source=Inms&tbm=isch&sa=X&ei=3aJXU4CiCML1Of-DgbgP&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=1yH3bRIVA0QwHM%253A%3B-RQIDexWQSdwaM%3Bhttp%253A%252F%252Fwww.cancer.gov%252Fimages%252Fcdr%252Ffive%252FCDR526219-571.jpg%3Bhttp%253A%252F%252Fwww.cancer.gov%252Fcantopics%252Fpdq%252Ftreatment%252FadultAML%252FPatient%252Fpage1%3B571%3B481

Cancer Research UK

<http://www.cancerresearchuk.org/cancer-help/type/cml/about/symptoms-of-chronic-myeloid-leukaemia>

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Leukaemia & Lymphoma Research

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<https://leukaemialymphomaresearch.org.uk/information/leukaemia/chronic-myeloid-leukaemia-cml/staging>

MacMillan Cancer Support

<http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Leukaemiachronicmyeloid/AboutCML/WhatisCML.aspx>

Mayo Clinic

<http://www.mayoclinic.org/diseases-conditions/chronic-myelogenous-leukemia/basics/prevention/con-20031517>
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Medicine.Net

<http://www.medicinenet.com/script/main/art.asp?articlekey=107515>

National Cancer Institute

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Uptodate

<http://www.uptodate.com/contents/chronic-myeloid-leukemia-cml-in-adults-beyond-the-basics>

<http://www.uptodate.com/contents/chronic-myeloid-leukemia-cml-in-adults-beyond-the-basics>

University of Rochester Medical Center

<https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=34&contentid=BCMLT13>

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