Hematology Cancer Consortium

CHRONIC MYELOID LEUKEMIA (CML)

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- **Introduction**

Blood and its cells are produced in the bone marrow.
Bone marrow is the place in the body where the components of blood-red blood cells, white blood cells, and platelets-are produced (Figure 1).

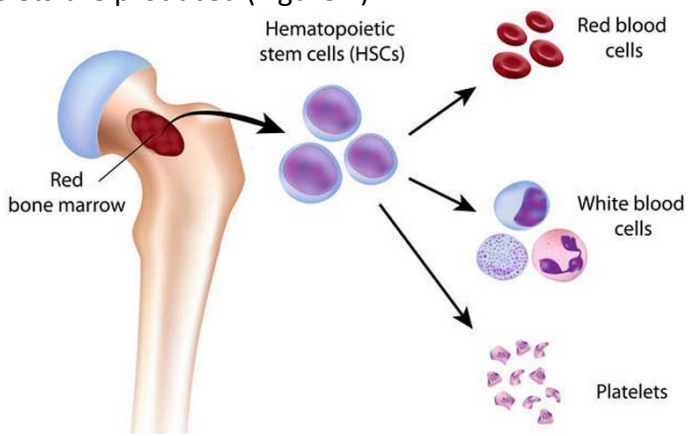

Figure 1: Schematic diagram to show blood cells production in bone marrow.

- **Know your Disease- CML**

What is CML?
Leukemia is a form of cancer, specifically, cancer of the blood. When Leukemia presents with rapid and stormy progression of symptoms, it is called as Acute Leukemia.
When the patient has slow course with symptoms developing over months to years, it is called as Chronic Leukemia.

Chronic myeloid leukemia (you may also hear the term *chronic myelogenous leukemia*) or CML, is a disease of the blood and bone marrow. It usually has slowly developing symptoms as characterised by chronic form of leukemias.

CML has evolved from a life-threatening disease to a well manageable disease in general, and if well treated, for most patients, CML is no longer the threat it once was. Majority of patients can be treated with oral medications and can survive as normal individuals.

CML has three phases, chronic phase, accelerated phase and blast phase. Majority of patients are diagnosed when they are in their phase of disease which is chronic phase. If not treated, this disease passes in severe phases of disease as time progresses. In patients who receive treatment, the chances of progression are totally avoided or are significantly delayed.

Who is affected by this disease?
CML is a disease of old age. It not unusual in our country to have CML in younger and middle aged adults. This disease can also very rarely be seen in children as well.

What causes the disease?

- All our cells have chromosomes which control how all our cells and organs should divide and function.

• In classical cases of CML, two chromosomes in blood forming cells inside the bone marrow break and reattach to the wrong chromosomes. This creates what is known as the Philadelphia chromosome. This is why this form of the disease is called Philadelphia chromosome-positive CML. It is often abbreviated as Ph+ CML or just CML (Figure 2)

• This abnormal Philadelphia (or Ph) chromosome exists in blood cells and does not function correctly. In Ph+ CML, the Ph chromosome carries a damaged gene called BCR-ABL. The damaged *BCR-ABL* gene creates a damaged protein which is also called BCR-ABL.

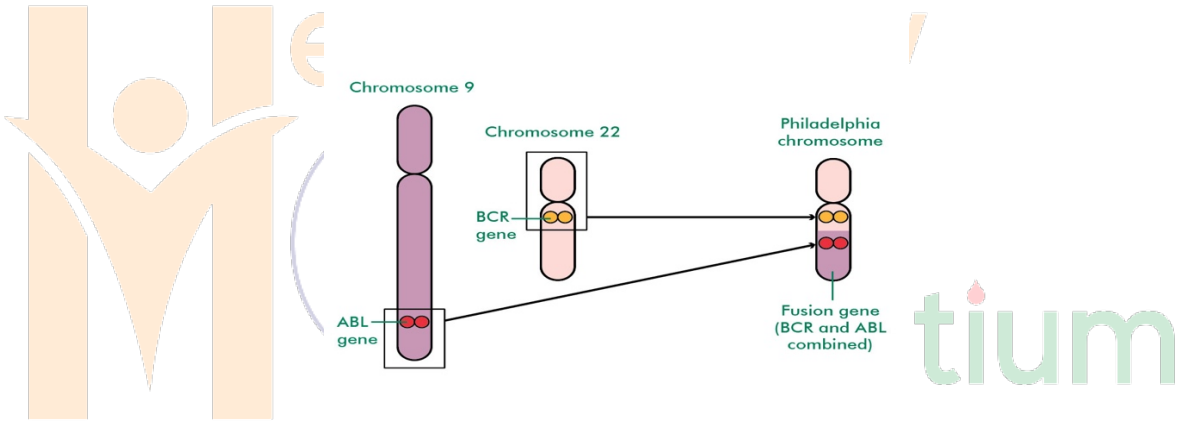

Figure 2: Formation of Philadelphia (Ph) Chromosome in CML

Think of the BCR-ABL protein like a light switch.

The damaged BCR-ABL protein "turns on" the bone marrow to make too many white blood cells. These abnormal white blood cells (also known as leukemic cells) crowd out normal healthy cells. If the damaged BCR- ABL protein were healthy and normal, it would send a signal to the bone marrow to turn on and off the production of white blood cells as needed.
The leukemic cells grow and divide, building up in the bone marrow, spilling over into the bloodstream and circulating through the body. In time, the cells can also settle in other parts of the body, including the spleen.

What are the symptoms of the CML?
As this disease is a chronic disease, sometimes CML patients may have no symptoms.
Diagnosis of such patient happen when blood is tested for some other reason.

In patients with symptoms, majority have fullness on left side of abdomen, unintended weight loss, fever, recurrent infections, bleeding tendency, loss of appetite, tiredness, etc.

- **Testing in CML for diagnosis and monitoring**

There are several different tests you will need to have throughout your CML treatment. Each test measures the amount of disease in your body in a different way. These tests can help evaluate if your CML treatment is working.

- Tests are taken at different times during the treatment process
- The most variety of testing will likely happen in the first 12 months after a diagnosis of Ph+ CML

Tests to diagnose CML -

Complete Blood Count (CBC)

CBC is the most basic test that your doctor will do for you. This test will tell you about the white blood cell count (WBC), hemoglobin and the platelet count. It can also give information on in which phase of disease the patient is currently in. Initially CBC is done every 15 days after starting of treatment and once the patient's cells come in normal range i.e., patient achieves **Complete Hematological Response** then the testing is reduced to every 3 monthly.

Bone Marrow testing

Bone marrow is taken for testing at diagnosis to confirm the phase of disease and also to collect sample for Cytogenetic study which will be elaborated further.

1) Cytogenetic Study-

The sample collected from the bone marrow is subjected to cytogenetic study to confirm the presence of Philadelphia chromosome.. It also detects any additional problems in the chromosomes, which can predict the chance of long-term response to treatment. When Cytogenetic test comes negative while on treatment then the patient is said to have Complete Cytogentic Response (CCyR).

Polymerase Chain Reaction (PCR) (Molecular testing)

This test is very important test in diagnosis as well as to monitor treatment response. Only PCR testing is sensitive and clear enough to check for even the smallest number of leukemic cells. Blood or bone marrow sample can be used to do PCR test. **PCR is the ONLY test that can find one Ph+ CML cell among 1 million normal cells.**

This test is performed at time of diagnosis, after that every 3 months to track your progress by measuring your BCR-ABL levels down to 0.1%, as recommended by medical guidelines. When BCR-ABL levels reach ≤0.1%, a **Major Molecular Response** (MMR) has been achieved. After achieving ≤0.1%, it is recommended that you continue getting PCR tests done every 3 to 6 months while on treatment. If your BCR-ABL levels start to go up again, your doctor needs to know right away.

- **Know the treatment- basics**

Twenty years ago, treatment of CML required chemotherapy and bone marrow transplant. The treatment of CML has now changed completely and can be managed with oral medicines called Tyrosine Kinase Inhibitors (TKIs). The first TKI that revolutionized the treatment of CML was Imatinib. Later various new TKIs were developed which are more potent like Nilotinib, Dasatinib, Bosutinib, Ponatinib etc. The choice of drug that needs to be initiated is decided by the treating doctor depending upon patient condition, risk status (e,g Sokal score), other illnesses, disease severity, patient preference and cost of therapy. Please discuss with your doctor about the choice of initial TKI to be started.

- **Know your response- Treatment Milestones**

Once treatment with a TKI is started, response to treatment is measured by a blood test called quantitative PCR (QPCR or RQPCR), which counts the number of abnormal cells still present in the blood. At each time point after treatment, a particular target has to be achieved. Typically, this test is done at 3, 6 and 12 months after treatment and a patient can fit into three categories based on response (Table 1). The target at 12 months is considered most important for predicting long term outcomes.

a. Optimal: This is the best response and the same medication is continued

b. Failure: When a drug fails to work, either because of nature of disease or development of resistance. Further testing will be done to decide which is the best treatment option as the same TKI will not be of any benefit.

c. Suboptimal: This is a response in between the above two and just requires more frequent testing. The drug may or may not be changed depending on further response

Table 1-Milestones for treating CML expressed as BCR-ABL1 on the International Scale (IS).

From: European Leukemia Net 2020 recommendations for treating chronic myeloid leukemia

	Optimal	Warning	Failure
At 3 months	≤ 10%	>10%	>10% if confirmed within 1–3 months
At 6 months	≤1%	>1–10%	>10%
At 12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%

MMR- Major Molecular Response (BCR-ABL1 ≤0.1% by QPCR testing on IS).

What if there is no response to initial treatment?

If you fail with the treatment started as per criteria given in the table 1, then testing for checking drug resistance is done. In some situations, bone marrow testing and other tests are performed, if you are suspected to have disease progression on CBC testing. After testing, a plan is made to change the drug to other best possible TKI. Sometimes giving injection chemotherapy and Bone marrow transplantation is also considered if required.

- **Know your treatment duration**

By default, you should consider treatment for CML to continue lifelong. However, there are a small group of patients who have a very good response to treatment in whom we can try to stop the TKI. This can be tried after a minimum interval of 3 years when your BCR/ABL1 is <0.01 (MR4) for at least two years. In approximately 50% of these patients, the disease will stay in control after stopping medication.

This has to be done strictly under supervision of the treating physician who will assess whether you qualify for stopping treatment. For a majority of patients, treatment has to be continued lifelong.

- **Special Issue- Pregnancy**

For female patients with CML it is not recommended to get pregnant while on TKI therapy. It has shown to have detrimental effect on the foetus. If you have very good response which is better than MMR (called as DMR) for at least 2 years, attempt to stop the TKI and consideration for pregnancy can be given. In other individuals shifting to safer options like interferon therapy before conceiving needs to be discussed with your treating doctor.

For a male patient with CML, very little data is present on effect of TKI on pregnancy. Although it is generally considered safe, please discuss with your doctor before planning a pregnancy while on treatment.

Glossary

BCR-ABL gene– The faulty gene created by the Philadelphia chromosome, which creates the BCR-ABL protein. The BCR-ABL protein acts as a messenger that sends an incorrect instruction to the bone marrow. This incorrect instruction tells the bone marrow to produce too many white blood cells.

Bone marrow– The soft, sponge-like tissue that is found inside the hard, outer covering of some bones. The bone marrow is the body's factory for making red blood cells, white blood cells, and platelets.

Chromosome– A part of the cell that carries genetic information or genes.

Chronic– A lasting or slowly progressing disease, or one in which the damaged cells grow slowly.

Chronic myeloid leukemia (CML)– A form of cancer of the white blood cells that generally develops slowly. In CML, the bone marrow makes too many white blood cells, many of which are damaged.

Complete blood count (CBC)– A test of the blood that includes a count of red blood cells, white blood cells, and platelets.

Complete cytogenetic response (CCyR)– The BCR-ABL gene is less than 1% when measured on the International Scale.

Complete hematologic response (CHR)– When blood cell counts return to normal, there are no immature cells seen in the blood, and the spleen has returned to normal size.

Cytogenetic test– A test done on bone marrow cells or white blood cells to see if they contain the Philadelphia chromosome.

Deep molecular response (DMR)– The amount of BCR-ABL in the body has decreased to MR4 (molecular response 4) or deeper.

Disease progression– The course of a disease, such as cancer, as it becomes worse or spreads in the body.

Gene– A set of coded instructions in cells needed to make new cells and control how cells behave.

Leukemia– A cancer of the bone marrow and the blood in which large numbers of damaged white blood cells are produced and released into the blood, crowding out healthy blood cells.

Major molecular response (MMR)– This means that the amount of BCR-ABL gene found in the bone marrow sample or blood sample through the standardized PCR test (≤0.1%).

Milestone– an event marking a significant change or development. Treatment milestone for CML means that a new level in reduction of the amount of disease in the body has been reached. Milestones are set by medical guidelines.

PCR test– A very sensitive test to count the number of cells that have the BCR-ABL gene (which is found on the Philadelphia chromosome).

Ph+ CML– The abbreviation of Philadelphia chromosome-positive chronic myeloid leukemia.

Philadelphia chromosome– A faulty or damaged chromosome that is found in the leukemic cells of nearly all people (95%-100%) with chronic myeloid leukemia.

Platelet– Very small cells found in the bone marrow that help stop bleeding from happening by causing blood to clot.

Protein– Proteins are the building blocks of the body. They are made by genes and often act as messengers.

Red blood cell– A kind of blood cell that is responsible for carrying oxygen around the body.

Sokal score– A scoring system used to predict a person's likelihood of response to treatment. It measures age, spleen size, platelet count, and the amount of leukemic cells in the patient's blood to calculate a risk score that is helpful when making treatment decisions.

White blood cell– A blood cell made by the bone marrow and involved in the body's immune response

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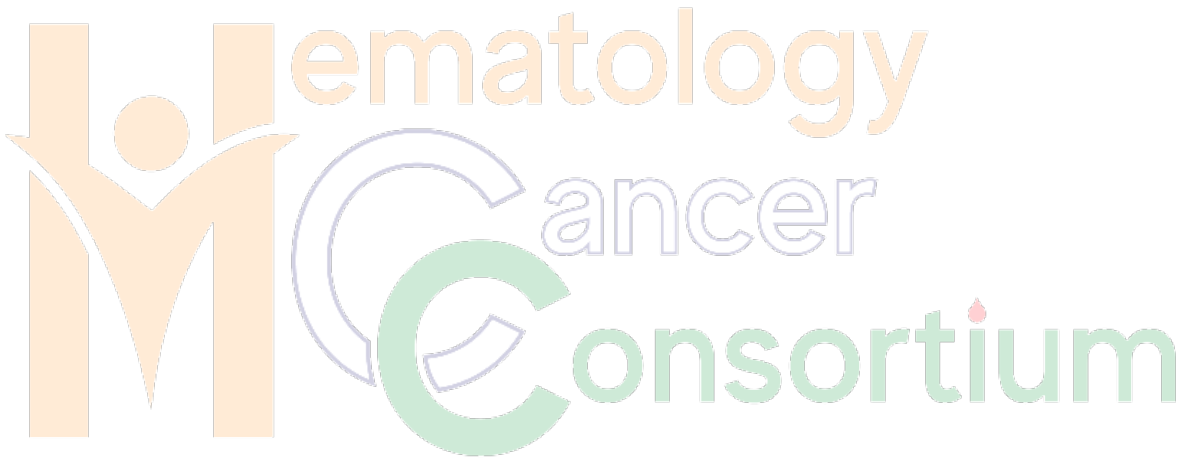
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