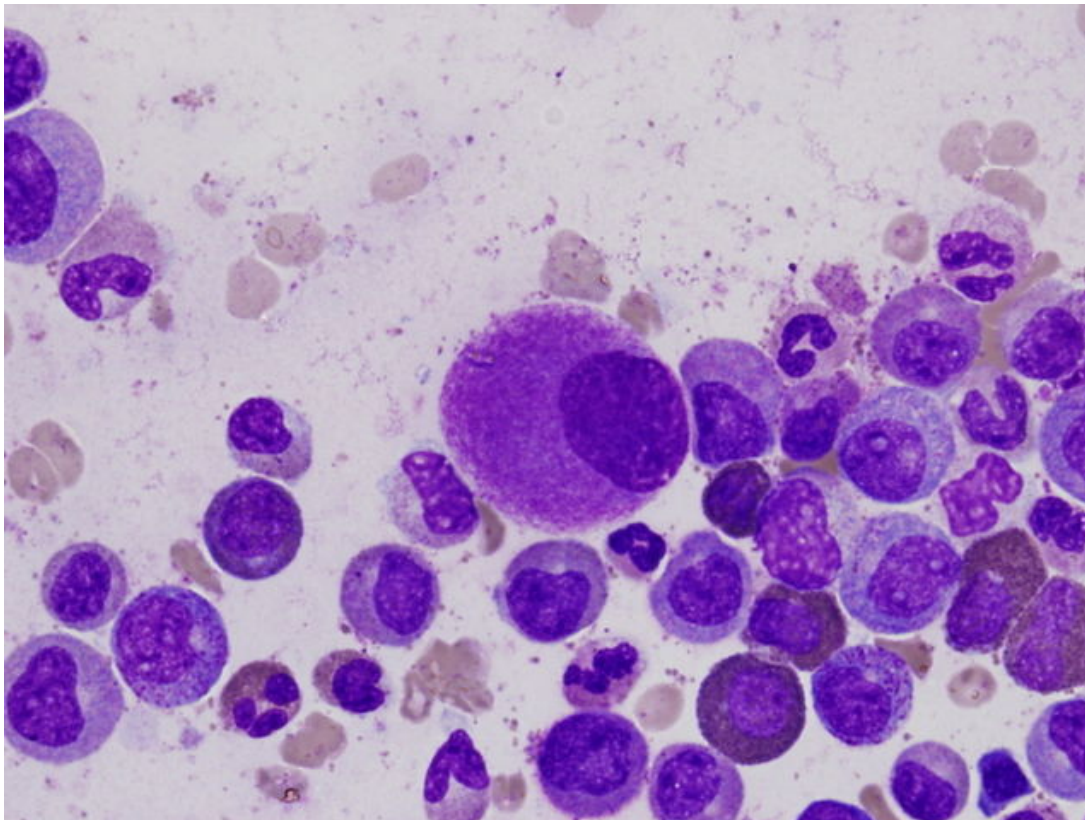


Chronic Myeloid Leukemia (CML) — Classification and Staging

[See online here](#)

Chronic myelogenous leukemia, also called chronic myeloid leukemia (CML), is an acquired monoclonal expansion of white blood cells of myeloid lineage. It is common in middle and old age accounting for 20% of adult leukemia. It is sometimes diagnosed incidentally on routine blood investigations or the presence of splenomegaly on examination. CML is classically associated with the Philadelphia chromosome (BCR-ABL fusion gene) and has an excellent prognosis with modern therapy.



Definition of CML

What is chronic myeloid leukemia (CML)?

Chronic myelogenous leukemia, also called **chronic myeloid leukemia (CML)**, is an acquired monoclonal proliferation of white blood cells (WBCs) of myeloid lineage. The cells are terminally differentiated and mature appearing, in contrast to the immature (blast) cells of [acute myeloblastic leukemia](#). It is classically associated with the **Philadelphia chromosome** (BCR-ABL fusion gene).

Background and Classification of Myeloid Neoplasms

CML and other types of leukemia:

1. Acute myeloblastic leukemia
2. Myelodysplastic syndrome
3. Chronic myeloproliferative disorders
 - a. Polycythemia vera
 - b. Essential thrombocytosis
 - c. Myelofibrosis
 - d. Chronic, myelogenous leukemia

The hematopoietic stem cells are present within the bone marrow, derived from the **mesoderm**, and produce all the blood cells. The stem cells proliferate and divide into 2 **blood cell** lineages, the myeloid lineage, and the lymphoid lineage.

- The myeloid lineage consists of granulocytes (neutrophils, basophils, and eosinophils), monocytes, mast cells, red blood cells (RBCs), and the platelets.
- The lymphoid lineage includes B cells, T cells, and natural killer (NK) cells.

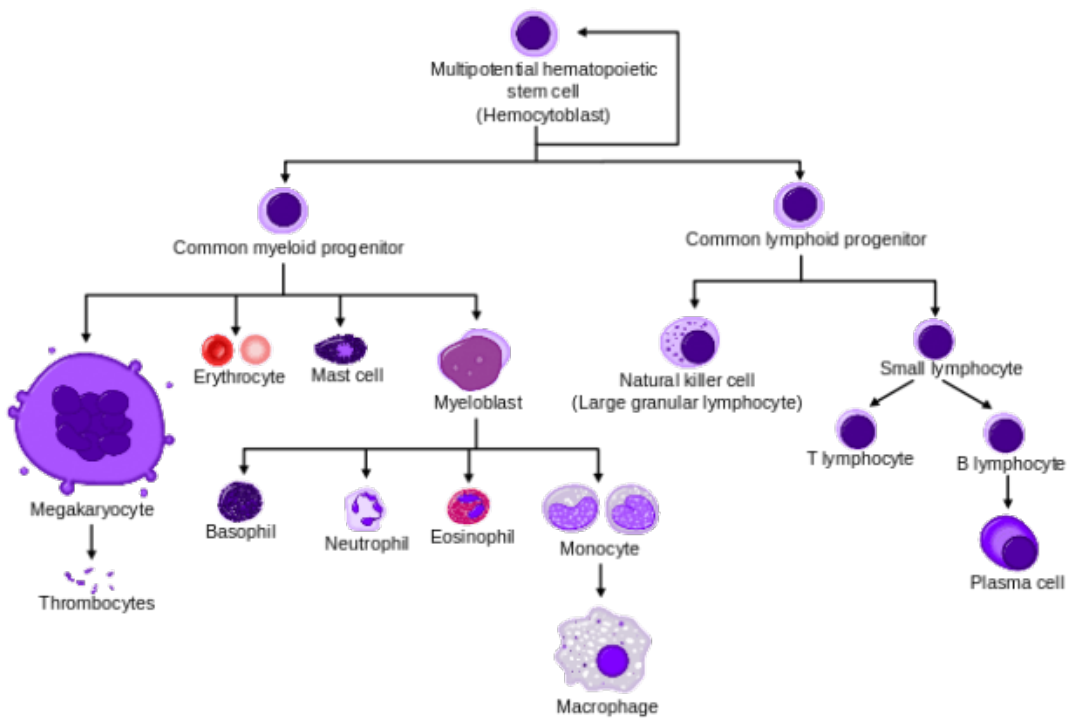


Image: Hematopoiesis simple. By A. Rad, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The myeloid neoplasms are derived from the myeloid cell lineage and are divided into 3 general categories:

Acute myeloblastic leukemia (AML): It is an acute proliferation of **myeloid cell lineage** with a preponderance of the immature (blast) cells within the bone marrow, which are also spilled into the peripheral blood.

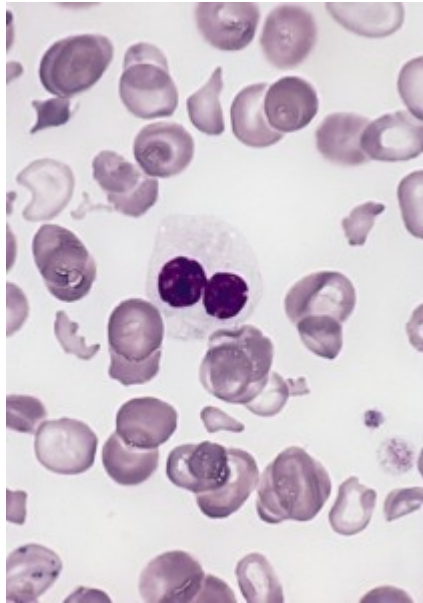


Image: A hypogranular neutrophil with a pseudo-Pelger-Huet nucleus is shown." by The Armed Forces Institute of Pathology (AFIP), License: Public Domain.

Myelodysplastic Syndrome: It is a pre-leukemic syndrome characterized by abnormal morphology (dysplasia) of myeloid cells. E.g., the granulocytes have decreased intracytoplasmic granules. The neutrophils have only 2-lobed nuclei, called **Pelger-Huet cells**. The **megakaryocytes** are dwarfed. The RBCs are large, oval and show ringed sideroblastic iron staining pattern. Because of such abnormal shapes, these cells are destroyed before being released into the peripheral blood circulation, leading to cytopenias and hypercellular bone marrow.

Chronic myeloproliferative disorders: These disorders consist of a chronic proliferation of myeloid cell lineage and are terminally **differentiated mature-appearing cells**. There is usually an increase in 1 or more types of myeloid cells, such as a predominant increase in RBCs, or platelets, or WBCs. Therefore, they are further subdivided into 4 groups based on a predominantly affected myeloid blood cell.

- Polycythemia vera: The **chronic neoplastic proliferation** of RBCs with hematocrit commonly exceeding 60%. WBCs and platelets may or may not increase concomitantly.
- Essential thrombocytosis: The chronic neoplastic proliferation of platelets with platelet counts increasing as high as 2,000,000/mcL. WBCs and RBCs may or may not increase concomitantly.
- Myelofibrosis: This myeloproliferative disorder is characterized by excessive **fibrosis of bone marrow** with teardrop RBCs, **splenomegaly and leukoerythroblastic** peripheral blood picture. The increased **platelet-derived growth factor (PDGF)** secreted by proliferating megakaryocytes is responsible for excessive fibrosis.
- Chronic myelogenous leukemia (CML): The chronic neoplastic proliferation of WBCs of myeloid lineage.

These 4 disorders are also grouped because they have an increased association with abnormal tyrosine kinases in their pathogenesis. The mutated Janus kinase 2 (**JAK-2 kinase**) is present in the 1st 3 disorders, while CML is classically associated with the Philadelphia chromosome, which also activates a tyrosine kinase and is discussed later.

Epidemiology of CML

Incidence of CML

CML is common in middle and old age people, accounting for around 20% of all adult leukemia cases. The median age of presentation is 55 years.

In the United States, the incidence is around 1.5 cases per 100,000 inhabitants with approx. 5,500 new cases diagnosed in 2012. The incidence increases with age and is slightly more common in males.

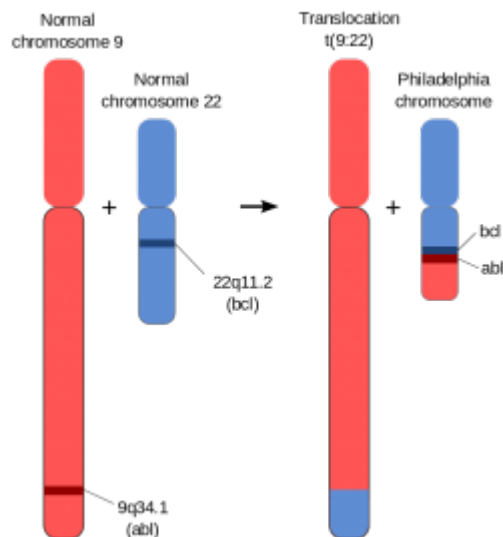
Etiology of CML

Reasons for CML

In most of the CML cases, the etiology is not known. The high dose ionizing radiation is considered an important risk factor as an increased incidence of CML was seen in survivors of the Hiroshima and Nagasaki atomic bombs.

Pathophysiology of CML

CML is classically associated with the presence of an acquired genetic abnormality, **BCR-ABL fusion gene**. ABL is a proto-oncogene named after Abelson murine leukemia virus, while BCR stands for the breakpoint cluster region. The BCR-ABL fusion gene has tyrosine kinase activity and is responsible for the uncontrolled proliferation of the cells.



[Image](#): Schematic of the Philadelphia Chromosome. By Aryn89, License: [CC BY-SA 4.0](#)

In 95% of the cases, this BCR-ABL fusion gene is formed due to the translocation of the ABL gene from chromosome 9 to the BCR gene on chromosome 22, t(9;22). This newly formed chromosome 22 having the BCR-ABL fusion gene is called the '**Philadelphia chromosome**'. It is named after the city where it was 1st discovered.

It should be remembered that the Philadelphia chromosome, though characteristically

associated with CML, is not restricted to CML only. It is also present in **acute lymphoblastic leukemia (ALL)**, and rarely in **acute myeloblastic leukemia (AML)**.

Staging of CML

Phases of CML

The World Health Organization (WHO) has divided the **CML** into 3 progressive stages based on the aggressiveness of the disease, response to therapy, and the presence of blasts. These are as follows:

1. Chronic stable phase

It is the most common indolent clinical phase of CML. This phase is stable and lasts for many years. The myeloid cells are differentiated, with a presence of less than 10% of blast cells. The response to therapy is excellent.

2. Accelerated phase

The untreated CML usually progresses to the accelerated phase. The cells multiply aggressively and the blast cells increase in the blood usually between 10–19%. The response to therapy is poor.

3. Blast crisis

The accelerated phase progresses to the blast crisis. This phase is indistinguishable from acute leukemia with blast cells more than 20%. The response to therapy is very poor.

Clinical Presentation of CML

Symptoms of CML

In the early chronic stable phase, CML does not behave like a malignant disease. Quantitatively WBCs are increased, but they are differentiated and mature, and combat the infections. Patients may present with non-specific symptoms of **low-grade fever, malaise, night sweats, or abdominal fullness**, and early satiety due to an enlarged [spleen](#).

Spleen size roughly correlates with the WBC count and massive **splenomegaly** corresponds to poor prognosis. **Hepatomegaly** is also common, but **lymphadenopathy** is usually not present. In 25% of cases, patients are asymptomatic and CML is diagnosed on routine blood tests or **palpable spleen** on physical examination.

In the accelerated phase and blast crisis, the patient presents with acute leukemia-like **fever, bleeding, petechiae, ecchymosis, and pallor** due to over-expansion of bone marrow with the blast cells and ineffective production of platelets and RBCs. The patient may also have bone tenderness and **splenomegaly** due to extra-medullary **hematopoiesis**.

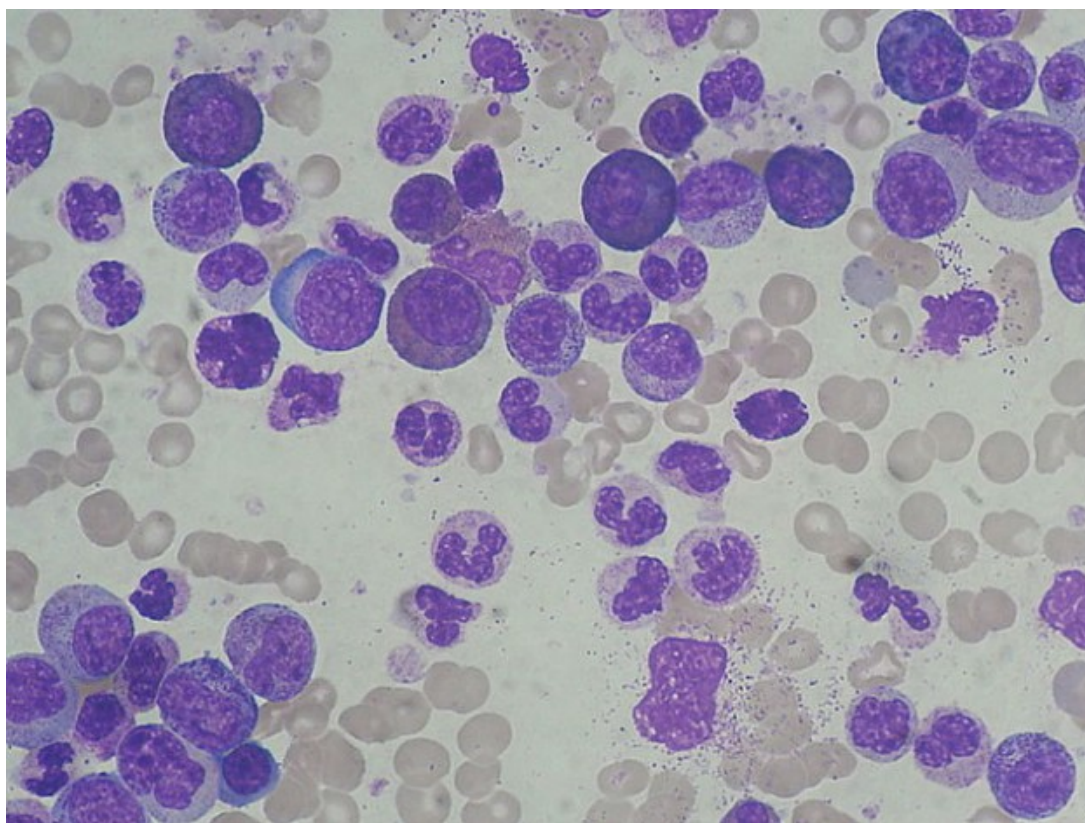
Rarely, patients may present with symptoms of **leukostasis** such as confusion, blurred vision, [respiratory distress](#), thrombosis, headache or priapism, with WBC count usually > 500,000/mcL. It is a medical emergency and should be urgently treated with

leukapheresis and **judicious hydration**.

Laboratory Evaluation and Diagnosis of CML

Methods for diagnosing CML

Complete blood count (CBC) is the initial investigation. It shows an increase in the WBCs, predominantly in the myeloid series. The WBC count ranges from 10,000-600,000/mcL. The cells are mildly left-side shifted with an increase in **myelocytes**, **meta-myelocytes**, and **pre-myelocytes**, but the blast cells are usually less than 10% unless the patient presents with accelerated or blast crisis. **Basophils** and **eosinophils** are also elevated. **Hematocrit** is usually normal with normal RBC morphology. Platelets are usually increased.



[Image](#): Chronic myeloid leukemia (CML): marked leucocytosis with granulocyte left shift. By Paulo Henrique Orlandi Mourao, License: [CC BY-SA 3.0](#)

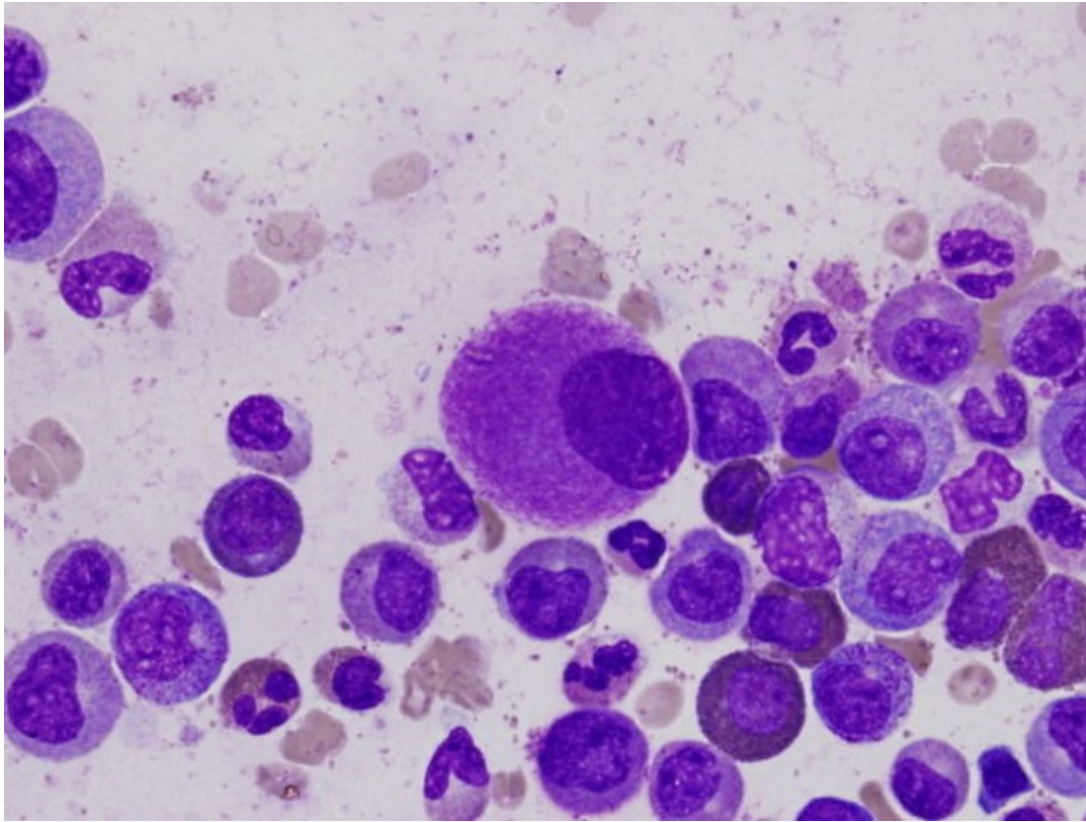


Image: A small, hypolobated megakaryocyte in a bone marrow aspirate, typical of chronic myelogenous leukemia. By Difu Wu, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Karyotyping will reveal the presence of Philadelphia chromosome t(9;22).

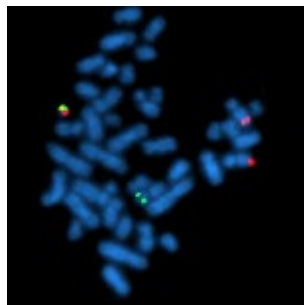


Image: BCR-ABL is detected by FISH. The chromosomes are in blue. The separate red color (on the right) and separate green color (in the middle) on chromosomes show BCR and ABL on their respective chromosomes unfused; but the chromosome that shows the green-red fused color in the upper left corner shows the BCR-ABL gene rearrangement. By Pmx, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The specific genetic abnormality BCR-ABL will be detected by a polymerase chain reaction (PCR) or by **fluorescence in-situ hybridization (FISH)** methods.

The characteristic CBC findings with the presence of the **Philadelphia chromosome/BCR-ABL fusion gene** form the peripheral blood confirm the diagnosis. Bone marrow examination is usually not required. The bone marrow examination can be done in equivocal cases, to look for other chromosomal abnormalities or to assess the

prognosis of the disease.

The **leukocyte alkaline phosphatase (LAP) score** may be used if the diagnosis is confused with reactive **leukocytosis**, in which WBCs are increased in response to infectious or inflammatory conditions. In CML, the LAP score is low, while in reactive leukocytosis, the LAP score is high.

Treatment of CML

Possible therapy for CML

The treatment goals for CML are as follows:

1. Hematologic remission: normalization of blood counts and **splenomegaly**
2. Cytogenetic remission: the disappearance of the **Philadelphia chromosome** on karyotyping
3. Molecular remission: negative **PCR/FISH** for BCR-ABL fused gene

The discovery of specific **tyrosine kinase inhibitors**, such as **imatinib, dasatinib, and nilotinib**, has revolutionized the treatment and prognosis of **chronic myelogenous leukemia**. They inhibit the BCR-ABL specific tyrosine kinase and cause apoptosis of these cells. These drugs are well-tolerated and achieve the **hematologic remission** of the chronic phase of CML in 95% of cases and complete **cytogenetic remission** in 76% of cases after 18 months of treatment, but the molecular remission is achieved in only 26% of cases. These drugs also delay the progression of the chronic phase of CML to the accelerated phase and blast crisis, but they should be taken continuously as their discontinuation leads to relapses.

In newly diagnosed CML, the prognostic milestones are set to achieve complete **hematologic remission** in 3 months and the complete **cytogenetic remission** in 18 months of treatment. If these are not achieved, the treatment regimen has to be re-assessed.

In an accelerated and blast crisis, there is a much lower response to **imatinib** and related drugs. In these cases, higher doses of drugs are given and bone marrow transplantation is advised to cure the disease. The supportive therapy with empiric **antibiotics**, **RBCs**, and **platelet transfusions** may also be needed.

Bone marrow transplantation

The **allogeneic bone marrow transplantation (BMT)** is the only proven cure for CML. Ideally, it should be offered to all the candidates if a matched donor is found, but the promising results of imatinib and related drugs have limited the BMT to individuals with poor prognosis and treatment resistance.

Other treatments

- **Interferon-alpha** was previously the 1st-line drug to manage CML. Interferon-alpha is still given in an accelerated phase/blast crisis in combination with imatinib and the imatinib-resistant cases.
- **Hydroxyurea and busulfan** are anticancer drugs that decrease the blood cell count for palliation without affecting the **Philadelphia chromosome** or progression to accelerated phase/blast crisis.

- Splenectomy may be done for palliation in patients with late-stage CML complaining of pain and discomfort due to the enlarged spleen and splenic infarcts.

Tumor lysis syndrome

It is a collection of metabolic derangements that occur during cancer treatment. The rapid killing of leukemic cells releases the intracellular contents into the blood circulation which causes **hyperuricemia, hyperkalemia, and hyperphosphatemia**, and may lead to fatal acute renal injury.

It should be managed promptly by judicious hydration and allopurinol or rasburicase. **Allopurinol** is a xanthine oxidase inhibitor that decreases the production of uric acid. **Rasburicase** converts the insoluble uric acid to soluble allantoin promoting its excretion. Sodium bicarbonate may be used to alkalinize the urine to increase uric acid excretion.

Prognosis and Survival of CML

Chances of surviving CML

The prognosis and survival are dependent on several factors and should be made on an individual basis. Generally, the median survival age of CML was around 4 years in the pre-imatinib era. The adequate treatment with imatinib increases the 5-year survival rate of chronic phase CML to more than 90%. Patients with accelerated phase/blast crisis have a very poor outcome and it is the major cause of death with an average survival of less than 1 year.

Some of the poor prognostic factors of CML are as follows:

- Old age
- Absence of **Philadelphia chromosome/BCR-ABL fused gene**
- Increase blasts (accelerated phase/blast crisis)
- Delay in achieving hematologic remission
- The short duration of hematologic remission
- **Splenomegaly**
- Anemia
- **Thrombocytopenia/thrombocytosis**
- **Basophilia**

Long Term Monitoring of CML

Follow-up treatment for CML

The CML patients require a long term follow-up for assessing the prognosis, relapses, the treatment side effects and monitoring the overall health, even after the bone marrow transplantation.

The **karyotyping** is performed every 3-6 months to assess the cytogenetic response by counting the percentage of **Philadelphia-chromosome** positive cells. As previously discussed, the complete **cytogenetic remission** is usually achieved after 18 months of treatment. The failure to achieve this leads to the re-assessment of the treatment regimen.

The common side effects of imatinib are nausea, [skin rashes](#), fluid retention, [diarrhea](#), and muscle cramps. The **myelosuppression** rarely occurs and may require the holding of the drug, if severe.

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