Chronic Myeloid Leukemia (CML) — Classification and Staging

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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 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 of myeloid lineage. The cells are terminally differentiated and mature appearing, in contrast to the immature (-blasts) cells of acute myeloblastic leukemia. It is classically associated with the Philadelphia chromosome (BCR-ABL fusion gene).
Background and Classification of Myeloid Neoplasms

Chronic myeloid leukemia 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 two blood cell lineages, the myeloid lineage and the lymphoid lineage.

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

Acute myeloblastic leukemia (AML): It is an acute proliferation of myeloid cell lineage with a preponderance of the immature (-blasts) cells within bone marrow, which are also spilled into the peripheral blood.
Myelodysplastic Syndrome: It is a pre-leukemic syndrome characterized by abnormal morphology (dysplasia) of myeloid cells. For example, the granulocytes have decreased intracytoplasmic granules. The neutrophils have only two-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 releasing into the peripheral blood circulation, leading to cytopenias and hypercellular bone marrow.

Chronic Myeloproliferative Disorders: These disorders consist of chronic proliferation of myeloid cell lineage and are terminally differentiated mature-appearing cells. There is usually an increase in one or more types of myeloid cells, such as predominant increase in red blood cells, or platelets, or white blood cells. Therefore, they are further subdivided into four groups on the basis of predominantly affected myeloid blood cell.

- Polycythemia Vera: The chronic neoplastic proliferation of red blood cells 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 red blood cells may or may not increase concomitantly.
- Myelofibrosis: This myeloproliferative disorder is characterized by excessive fibrosis of bone marrow with tear drop RBCs, splenomegaly and leukoerythroblastic peripheral blood picture. The increased platelet-derived growth factor (PDGF) secreted by proliferating megakaryocytes is responsible for the excessive fibrosis.
- Chronic Myelogenous Leukemia (CML): The chronic neoplastic proliferation of white blood cells of myeloid lineage.

These four disorders are also grouped together because they have an increased association with abnormal tyrosine kinases in their pathogenesis. The mutated JAK-2 kinase is present in the first three disorders, while CML is classically associated with Philadelphia chromosome, which also activates a tyrosine kinase and is discussed later.
Epidemiology of CML

Incidence of Chronic Myeloid Leukemia

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 USA, the incidence is around 1.5 cases per 100,000 inhabitants with approximately 5500 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 increased incidence of CML was seen in survivors of Hiroshima and Nagasaki atomic bombs.

Pathophysiology of CML

Chronic myelogenous leukemia 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 break point cluster region. The BCR-ABL fusion gene has tyrosine kinase activity and is responsible for the uncontrolled proliferation of cells.

In 95% of cases, this BCR-ABL fusion gene is formed due to the translocation of ABL gene from chromosome 9 to the BCR gene on chromosome 22, t(9;22). This newly formed chromosome 22 having BCR-ABL fusion gene is called the “Philadelphia chromosome”. It is named after the city where it was first 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 Chronic Myeloid Leukemia**

The World Health Organization (WHO) has divided the chronic myelogenous leukemia into three 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 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 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 the 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 accelerated phase and blast crisis, the patient presents like acute leukemia with **fever**, **bleeding**, **petechiae**, **ecchymosis** and **pallor** due to overexpansion of bone marrow with the blast cells and ineffective production of platelets and red blood cells. 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 \textit{leukapheresis} and \textit{judicious hydration}.

Laboratory Evaluation and Diagnosis of CML

Methods for Diagnosing CML

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

\textbf{Image}: “Chronic myeloid leukemia (CML): marked leucocytosis with granulocyte left shift.” by Paulo Henrique Orlandi Mourao. License: \texttt{CC BY-SA 3.0}
The Karyotyping will reveal the presence of Philadelphia chromosome t(9;22).

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 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 Chronic Myeloid Leukemia

The treatment goals for CML are as follows:

1. Hematologic remission: Normalization of blood counts and splenomegaly.

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 chronic phase 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 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 the 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 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**, **red cell** and **platelet transfusions** may also be needed.

### Bone Marrow Transplantation

The **allogeneic bone marrow transplantation (BMT)** is the only proven cure of 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 first-line drug to manage CML. Interferon alpha is still given in accelerated phase/blast crisis in combination with imatinib and in the imatinib-resistant cases.
- **Hydroxyurea and busulfan** are anticancer drugs which 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 the cancer treatment. The rapid killing of leukemic cells releases the intracellular contents into the blood circulation which causes **hyperuricemia**, **hyperkalemia**, **hyperphosphatemia** and may lead to fatal acute renal injury.

It should be timely managed 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 is 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
- 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 treatment regimen.

The common side effects of imatinib are nausea, **skin rash**, fluid retention, **diarrhoea**
and muscle cramps. The myelosuppression rarely occurs and may require the holding of the drug, if severe.

**Review Questions**

The correct answers can be found below the references.

1. A 72-year old female is diagnosed with chronic myelogenous leukemia. She asks for her prognosis. Which of the following factors indicate a ‘good’ prognosis?

   A. Her age  
   B. Presence of Philadelphia chromosome  
   C. Splenomegaly  
   D. Basophils more than 20%  
   E. Platelet count of 55,000/mcl

2. A 59-year-old female presents with fever. Her CBC shows WBC count of 38,000/mcl with predominant granulocytes. You are confused whether it is reactive leukocytosis or chronic myelogenous leukemia. Which of the following findings will be in favor of CML?

   B. Less than 10% blast cells  
   C. Eosinophilia  
   D. Left side shift with presence of metamyelocytes and pre-myelocytes.  
   E. Low LAP (Leukocyte Alkaline Phosphatase) score  
   F. Splenomegaly

3. Which of the following chromosomal abnormalities is present in the Philadelphia chromosome?

   A. Chromosomal translocation t(11;14)  
   B. Chromosomal translocation t(8; 14)  
   C. Chromosomal translocation t(9;22)  
   D. Robertsonian translocation 22  
   E. Chromosomal deletion 5q-

**References**


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Correct answers: 1B, 2D, 3C

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