CHAPTER

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Chronic Myeloid Leukaemia – An Overview

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BACKGROUND

Chronic myeloid leukaemia (CML) is an acquired genetic defect in the pleuripotent stem cell that is characterised by leucocytosis with granulocytic immaturity, basophilia, splenomegaly and a distinct genetic abnormality BCR-ABL fusion gene, Philadelphia(Ph^+) chromosome [t(9;22)(q34;q11.2)].

EPIDEMIOLOGY

According to the western literature, the annual incidence of CML is around 1.8 per 100,000. In India, it accounts for 50 – 70% of leukaemias with an annual incidence of 1-2 per 100,000. The median age of presentation is around 40 years. CML accounts for 15 - 20% of all leukaemias affecting the adults with M:F ratio 1.6:1.

CLINICAL MANIFESTATIONS

The clinical findings of CML vary and depend upon the stage of disease at diagnosis. 20-50 % of patients are asymptomatic, diagnosed from routine blood tests.

Signs and symptoms

- Fatigue, weight loss.
- Low-grade fever, excessive sweating from hypermetabolism.
- Early satiety due to splenomegaly.
- Left upper quadrant abdominal pain from spleen infarction.
- Hepatomegaly.
- Appearance of palpable lymph nodes during the chronic phase indicates change to blast phase of the disease.

Investigations

1. PERIPHERAL BLOOD:

- Leucocytosis in all stages of maturation with myelocyte bulge (The presence of a greater percent of myelocytes than the more mature metamyelocytes ("leukemic hiatus" or "myelocyte bulge") is one of the classic findings in CML along with basophilia.
- Decreased LAP score– decreased (normal 40- 100). The low LAP score is useful in excluding a reactive leukocytosis or "leukemoid reaction," typically due to infection, in which the score is typically elevated or normal.

2. BONE MARROW FINDINGS: Markedly hypercellular with marked myeloid hyperplasia along with large histiocytes (pseudo gaucher cells) with blue granules and marrow fibrosis of variable degree.(reticulin strain)

CML has a triphasic or biphasic clinical course: a chronic phase(85%), an accelerated phase(<10%) and blast crisis(2-3 %).

Chronic phase

- Peripheral blasts <10% in the blood and bone marrow.

Accelerated phase

- Blasts 10-19% of white blood cells in peripheral and/or nucleated bone marrow cells.
- Persistent thrombocytopenia (< 100 × 10^9/L) or thrombocytosis (> 1000 × 10^9/L).
- Increasing WBC.
- Spleen size unresponsive to therapy.
- Cytogenetic evidence of clonal evolution

Blast phase

- Peripheral blasts ≥ 20% of white blood cells or nucleated bone marrow cells.
- Extramedullary blast proliferation.
- Large foci or clusters of blasts on bone marrow biopsy

Genetics :

Genetic testing for the Philadelphia chromosome, the BCR-ABL1 fusion gene or the fusion mRNA gene product is done by karyotyping, FISH analysis, or RT-PCR.

There are several distinct BCR-ABL1 fusion proteins depending upon the site of the breakpoint in the BCR gene on chromosome 22.

- The most common abnormal BCR-ABL1 fusion transcript is a BCR-ABL1 protein with 210 kilodalton molecular mass known as the p210 BCR-ABL1 protein.
- An alternative e19a2 fusion transcript is p230 BCR-ABL1. This is seen in rare CML cases (<1 %).
- A smaller e1a2 fusion transcript, which produces the p190 BCR-ABL1 protein is also seen in a very small number of CML patients, but is more

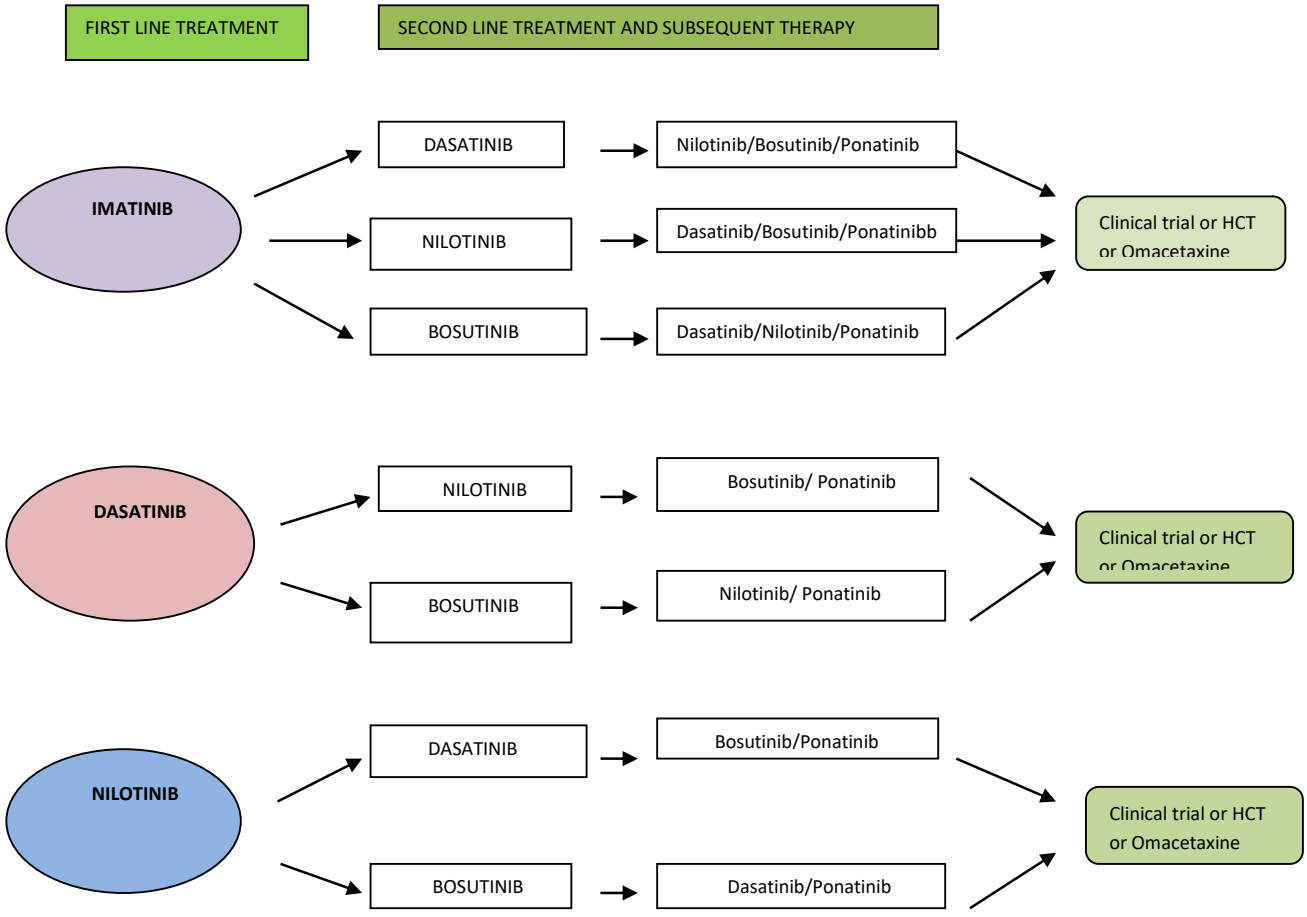

Fig. 1: Treatment of CML

Table 1: Treatment of Accelerated Phase

Tests before treatment	Treatment options	**Treatment of relapse**
BCR-ABL gene mutation analysis	1. TKI therapy (600 mg OD) 2. Omacetaxine 3. Consider HCT based on response	Clinical trial

frequently associated with Ph-positive acute lymphoblastic leukemia (ALL).

- The point mutation in BCR-ABL1 due to substitution of amino-acid at position 315 results in T3151 mutation which is implicated in the development of imatinib resistance.

DIFFERENCIAL DIAGNOSIS

- Leukemoid reaction.
- Juvenile myelomonocytic leukemia.
- Chronic myelomonocytic leukemia.
- Chronic eosinophilic leukemia
- Chronic neutrophilic leukemia
- Other Philadelphia chromosome positive malignancies.

TREATMENT

1 TYROSINE KINASE INHIBITOR THERAPY (TKI): (Figure 1)

- First generation : IMATINIB(400mg/d)
- Second generation : DASATINIB(100mg/d), NILOTINIB (300 mg BD), BOSUTINIB(500mg/d)
- Third generation : PONATINIB(45mg/d) (multitargeted TKI). It is only approved for patients with a T315I mutation or CML that is resistant to all other TKIs.

Common side effects of TKI therapy : Cytopenia, fluid retention, nausea and vomiting, muscle cramps, skin rash, diarrhea, headache, thyroid dysfunction, QT interval prolongation, hyperglycaemia (nilotinib), etc.

2. IMMUNOTHERAPY: Pegylated interferon may be used for those who cannot tolerate TKI therapy side effects. It is not used as an initial treatment option in patients of CML.

3. CHEMOTHERAPY: Omacetaxine was FDA approved in 2012 for treatment of CML for those with resistance and/or intolerance to two or more TKI. It is a protein synthesis inhibitor that has demonstrated activity in patients with CML in chronic phase with a T315I mutation. The recommended dose and schedule is 1.25 mg/m ^{2}

Table 2: Treatment of Blast Phase

Tests before treatment.	Cell lineage	Treatment options	Treatment of relapse
1. BCR-ABL mutation analysis 2. Cytochemistry	Lymphoid	1. ALL-type chemotherapy plus TKI (800 mg OD) followed by HCT if possible. 2. TKI followed by HCT if possible.	Clinical trial
	Myeloid	1. AML-type chemotherapy plus TKI (800 mg) followed by HCT if possible. 2. TKI followed by HCT if possible.	Clinical trial

Table 3

Type of Response	Definition
Hematological Response	WBC <10,000/microL with no immature granulocytes and <5 % basophils on differential; platelet count <450,000/microL and spleen not palpable.
Cytogenetic Response	
a. Complete cytogenetic response (CCgR)	No Philadelphia chromosome positive cells.
b. Partial cytogenetic response (PCgR)	1-35 % Philadelphia chromosome positive cells.
c. Major cytogenetic response (MCgR)	0-35 % Philadelphia chromosome positive cells
d. Minor cytogenetic response (mCgR)	36-65 % Philadelphia chromosome positive cells.
e. Minimal cytogenetic response (minCgR)	66-95 % Philadelphia chromosome positive cells.
f. No cytogenetic response (noCgR)	>95 % Philadelphia chromosome positive cells.
Molecular Response	
a. Major molecular response (MMolR)	Ratio of BCR-ABL transcript to housekeeping genes ≤0.1 percent (≥3 log reduction) on the international scale (IS).
b. Complete molecular response (CMolR)	BCR-ABL transcript nondetectable and not quantifiable in an assay that has at least 4 to 5 log range of detection on two consecutive blood samples.
Disease Response	**Monitoring Recommendation**
1. Hematological	1. At diagnosis. 2. Every 15 days till complete haematological response confirmed. 3. Atleast every 3 months or as needed thereafter.
2. Cytogenetic	1. At diagnosis. 2. At 3 and 6 months. 3. Every 6 months until complete cytogenetic response confirmed. 4. Every 12 months if uncertain about regular molecular monitoring. 5. At treatment failure or unexplained anaemia, leukopenia and/or thrombocytopenia.
3.Molecular(RT-PCR)	1. Every 3 months until major molecular response confirmed. 2. Atleast every 6 months thereafter.
4.Molecular (mutation analysis)	1. Suboptimal response or failure. 2. Before switching treatment.

subcutaneous injection twice daily for 14 days of a 28-day cycle for the induction phase and 1.25 mg/m ^{2} subcutaneous injection twice daily for 7 days of a 28-day cycle for maintenance.

Hydroxyurea (20 to 40 mg/kg/day) can be used to reduce white blood cell counts while awaiting confirmation of a suspected diagnosis of CML in a patient with significant leukocytosis (eg >100 x10 ^{9} white cells/L) or in patients with systemic symptoms or with symptomatic splenomegaly.

The treatment of Accelerated phase in given in Table 1 and Blast phase in Table 2. The type of response is given in Table 3.

4. ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT): High dose chemotherapy or radiation therapy followed by HCT is a treatment option for certain group of patients like unresponsive to TKI therapy, presence of T3151 mutation

5. DONOR LYMPHOCYTE INFUSION (DLI): It is procedure in which the patient receives lymphocytes from the same person who donated blood stem cells for HCT. The purpose of DLI is to stimulate an immune response called GVL (graft versus leukemia effect). It can be used after allogenic HCT for CML who didn't respond to the treatment or relapse after initial response.

6. CLINICAL TRIALS:

a. Combination therapy : TKI with chemotherapy or interferon or cancer vaccines.

b. Newer drugs :

- Farnesyl transferase inhibitors such as lonafarnib and tipifarnib.
- Histone deacetylase inhibitor panobinostat.
- Proteasome inhibitor bortezomib (Velcade).

c. Cancer Vaccines : The studies are being conducted on vaccines against CML called CMLVAX100. This, given along with imatinib seemed to increase its effectiveness.

TREATMENT OF CHRONIC PHASE

Best treatment options are TKI and HCT. HCT is the only curable option in CML. But TKI have demonstrated better long term disease control and good tolerability, hence they are preferred over HCT.

AIMS OF INITIAL THERAPY AND DURATION OF TREATMENT

- Complete hematologic response by 3-6 months.
- Any cytogenetic response by 6 months.
- Major cytogenetic response by 12 months.
- Complete cytogenetic response by 18 months

SUMMARY

HCT is only treatment curable option in CML but TKI therapy has revolutionized the management of CML. The need to overcome emergence of imatinib resistance has led to the investigation of combination therapies.

REFERENCES

1. Kantarjian H, Cortes J. Chronic Myeloid Leukemia. Kasper DL, Fauci AS, Hause SL, Longo DL, Jameson L, Loscalzo J. Harrison's principles of Internal Medicine. 19th ed. New York Mc Graw Hill Publishers 2015;687-695.
2. Deininger M. Chronic Myeloid Leukemia. Wintrobe's Clinical Hematology. 13th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins 2013;1705-1721.
3. Diseases of White Blood Cells, Lymph nodes, Spleen and Thymus. Kumar V, Abbas AK, Aster JC. Robbins & Cotran Pathological asis of Disease. 9th ed. Elsevier 2014;579-628.
4. Radich JP, Deininger M, Abboud CN, Altman JK, Barta SK, Berman E *et al* .Chronic Myeloid Leukemia. NCCN Guidelines for Patients. Version 1.2016;1-71.