Chronic Myeloid Leukemia in Childhood

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Abstract :

Introduction : Chronic myeloid leukemia (CML) is a myeloproliferative clonal disorder that originates in a pluripotent hematopoietic stem cell. **Epidemiology :** It is a rare malignancy of childhood. **Pathogenesis :** CML results from the balanced translocation t (9; 22) (q34; q11) that results in the fusion gene BCR-ABL. **Clinical features :** CML is a triphasic disease having chronic, accelerated and blastic crisis phases. Fatigue and abdominal pain are common complaints in childhood CML. Leukocytosis with shift to left, anaemia and splenomegaly are frequent findings. **Diagnosis :** CML is diagnosed in accordance with the WHO criteria. FISH or RT-PCR for BCR-ABL fusion is used for confirmation and monitoring treatment response. **Treatment :** Imatinib is the first line therapy and initiated along with hydroxyurea if the initial counts are high, and/or the patient presents with a high degree of hepatosplenomegaly. If it fails or is poorly tolerated second line TKIs may be tried as the mainstay of induction and maintenance therapy. Stem cell transplant is the only curative option, however, in the modern era Imatinib is the first choice of treatment. Role of cytotoxic chemotherapy is mainly palliative.

Key Words : Chronic myeloid leukemia, pediatric

Introduction :

Chronic myeloid leukemia (CML) is a myeloproliferative disorder. CML is a clonal disorder that originates in a pluripotent hematopoietic stem cell. It is characterized by myeloid hyperplasia of the bone marrow, extramedullary hematopoiesis and elevation of white blood cell (WBC) count (with appearance of the complete range of granulocyte precursor cells in the peripheral blood). CML bears specific cytogenetic marker that is known as the Philadelphia (Ph^+) chromosome.[1]

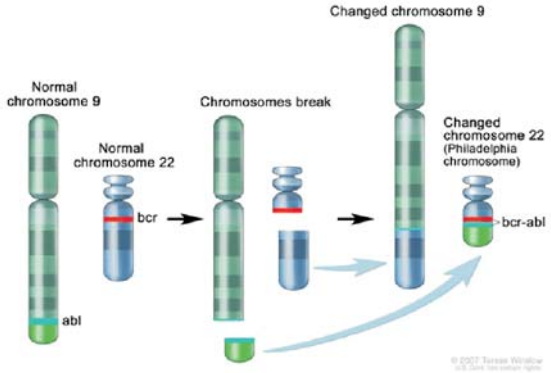
Epidemiology

Incidence of CML is described to be similar in all countries worldwide. It is mainly a disease of adults, having increasing diagnosis with advancing age. Chronic leukemias are rare in childhood and it is only 3% of pediatric leukemias, making evidence-based recommendations difficult. Other chronic leukemias in pediatric age group include juvenile chronic myelomonocytic leukemia, familial CML, chronic myelomonocytic leukemia, and chronic lymphocytic leukemia.[2]

Pathogenesis

The pathogenetic mechanism in pediatric and adult CML is same. The balanced translocation t(9;22)(q34;q11) results in the fusion gene *BCR-ABL*[3] that functions as a proto-oncogene (Fig.1). The Ph chromosome and BCR-ABL are found mainly in cells of the myeloid, erythroid, and megakaryocytic lineages, some B cells, and a small proportion of T cells, but not other cells of the body. The BCR-ABL fusion protein resides in the cytoplasm and has constitutive tyrosine kinase activity compared to the tightly regulated activity of the normal ABL product.[4,5] This activity either increases proliferation or decreases apoptosis of hematopoietic stem or progenitor cells, thereby, making CML a clonal disorder. This kinase pathway is of practical importance as tyrosine kinase inhibitors have been developed which target this constitutive tyrosine kinase activity.

Fig.1 : Philedelphia Chromosome



Picture Source:http://visualsonline.cancer.gov/details.cfm?imageid=7153
The (9;22) translocation transposes the ABL (Abelson) protooncogene from chromosome 9 into a relatively small, 5.8-kb genomic region on chromosome 22 named the breakpoint cluster region (bcr)

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Clinical Features

CML patients may have a triphasic clinical course. [1] The usual phase of the disease at the diagnosis (approximately 85 percent of patients) is "chronic phase" (CML-CP). With the accumulation of further mutations, CML-CP progresses to "accelerated phase" (CML-AP) as the malignant clone loses the capacity for terminal differentiation. The terminal stage of CML is "blast crisis" (CML-BC), a condition resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner. [1]

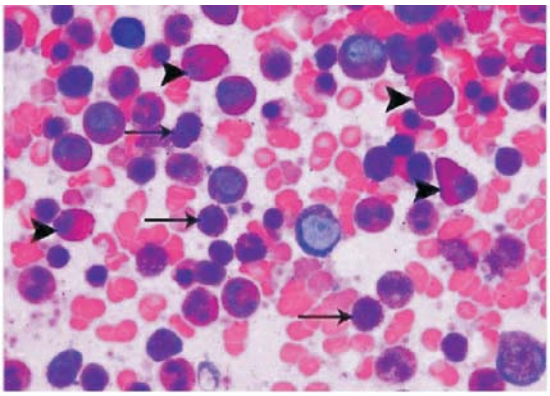
Twenty to fifty percent of adult patients may be asymptomatic and diagnosis of the disease first being suspected from routine blood tests. However the children commonly present with symptomatic complaints of fatigue, malaise, weight loss, excessive sweating, abdominal fullness, and bleeding episodes due to platelet dysfunction. Children with CML-CP typically have leukocytosis and anemia. In comparison to adults, children tend to present with higher WBC count (median WBC count of 2.5 lac). Symptoms in the accelerated phase or crisis can include fever, night sweats, rapid weight loss, splenic pain, lymphadenopathy, cutaneous infiltration, bleeding or infection. [6, 7, 8]

It is important how the sign of splenomegaly is approached in pediatric age group. The tip of the spleen is frequently palpable in children up to 3 or 4 years of age. At an older age, the spleen tip is generally not palpable below the costal margin and if it is palpable, usually indicates splenic enlargement two to three times than its normal size. In children, a palpable spleen may occasionally be due to visceroptosis rather than true splenomegaly. This distinction is important to make so that extensive investigations for the cause of splenomegaly are not undertaken unnecessarily.[9] Splenomegaly can be caused by diseases that result in hyperplasia of the lymphoid and reticuloendothelial systems (e.g., infections, connective tissue disorders), infiltrative disorders (e.g., Gaucher disease, leukemia, lymphoma), hematologic disorders (e.g., thalassemia, hereditary spherocytosis) and conditions that cause distention of the sinusoids whenever there is increased pressure in the portal or splenic veins (portal hypertension). [9]

The following are the hematologic findings [10] seen in CML (See Fig.2)

- Leukocytosis with shift to left
- Myeloid series in all stages starting from myeloblasts to segmented neutrophils
- Bone marrow hypercellularity

Fig.2 : Hematological Findings of CML



Bone marrow aspirate smear showing an increase in myeloid elements including basophils (Arrows) and eosinophils (arrowheads). Note that all stages of myeloid elements including a blast, promyelocytes, myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils. Monocytes do not appear be increased. This stage is called chronic stage. (PictureSource:http://www.pathpedia.com/education/eatlas/histopathology/bone_marrow/chronic_myelogenous_leukemia_%28cml%29.aspx)

Diagnosis

Diagnosis of CML should be in accordance to WHO criteria both in adult and pediatric patient. The primary diagnosis can be easily made by an experienced hematopathologist based on the morphology of cells in peripheral smear [10] (fig.2) and bone marrow. The morphological diagnosis should be confirmed with cytogenetic and molecular testing.

WHO criteria for diagnosis of CML-CP [11] are as follows,

- Leukocytosis with mature and immature granulocytes.
- Prominent dysgranulopoesis.
- Promyelocytes, myelocytes, metamyelocytes > 10% of WBC.
- Basophils < 2% of WBC.
- Monocytes < 10% of WBC.
- Hypercelluar marrow with granulocytic proliferation and dysplasia, with or without erythroid or megakaryocytic dysplasia.
- Less than 20% blasts in blood and marrow.

Besides these hematological feature, other abnormal laboratory investigations may include normocytic, normochromic anemia, increased absolute eosinophil and basophil count, thrombocytosis, decreased leukocyte alkaline phosphatase (LAP) score, deterioration of neutrophil function progressively elevation of lactic dehydrogenase and uric acid.

Genetic testing for the Philadelphia (Ph) chromosome is a must which establishes the diagnosis in conjugation with the cell morphology of marrow. Cytogenetic analysis of 20 marrow metaphases has been the standard method to detect the Ph chromosome and can diagnose 95% of patients. The remaining 5% with strong suspicious CML can be further diagnosed with fluorescence in situ hybridization (FISH) analysis, or by reverse transcription polymerase chain reaction (RT-PCR) for BCR-ABL fusion.

Factors[11] that adversely affect prognosis are age 50 years or older, increasing spleen size, increased percentage of blasts in the peripheral blood, eosinophils, basophils (3% or more), platelet count (1,500,000/µL or more).

Patients with CML usually pursue a normal lifestyle during the chronic phase. Any deviation from the stable pattern or new symptomatology may signal transformation into the acute phase or blastic crisis.[(11)] Symptoms or signs of the acute phase transformation may be;

- Anemia, thrombocytopenia, granulocytopenia, progressive basophilia, rising LAP score, or more rapidly increasing granulocytosis or erythroblastosis in a patient whose disease was previously under control
- Blasts ≥ 10% of bone marrow cells or peripheral WBC, or
- Extramedullary blast formation (e.g., osteolytic bone lesions, lymphadenopathy),
- Large foci or clusters of blasts in bone marrow.

Differential diagnosis

Differential diagnosis includes leukaemoid reaction, chronic myelomonocytic leukaemia, essential thrombocytosis and chronic neutrophilic leukaemia. These can be differentiated from CML by the absence of Ph chromosome or negative PCR for BCR-ABL.

Complications

Common complications that might occur or be the presenting feature of CML [(12)] include

1. Tumor lysis syndrome occurs usually with high WBC and is treated with hydration, recombinant urate oxidase (rasburicase) and allopurinol. Tumor lysis is rare in CML and usually only occurs in blast crisis or advanced accelerated phase.
2. Hyperleucocytosis leads to breathlessness, vision difficulty, headache, giddiness, improper circulation and priapism and treated with hydroxyurea (50–75 mg/kg/day) and/or leukapheresis. Leukapheresis is recommended when WBC >600,000/mm^3.

Treatment

Management of an adult CML patient is well established in a number of trials, either using imatinib, the first line tyrosine kinase inhibitor (TKI) or subsequent TKIs in case of failure. In treating pediatric age group, at times, the individualistic approach seems to be necessary as host properties do differ from adults but malignant clone's biologic features are identical to the adult CML.[(1)]

Treatment goals may be curative, control or palliation. Stem cell transplantation is the only curative option. In the pre Imatinib era, stem cell transplant was the only treatment available that would have cured a patient of CML. [(1)] Stem cell transplant is curative; but, it carries with it the disadvantage of significant morbidity and mortality. With the advent of first and second-generation oral tyrosine kinase inhibitors, current treatment of choice is imatinib that targets the constitutively active tyrosine kinase and achieves long-term control of CML in majority of patients. Hence TKIs are the initial treatment of choice for almost all newly diagnosed patients with CML. Imatinib received FDA approval for CML in adults in 2001 and in pediatrics in 2003. The usual starting dose of Imatinib is 340 mg/m^2/day. Dasatinib and nilotinib are second generation TKIs that more potent than imatinib. These have been recently approved for usage in imatinib resistance or intolerance [(13, 14)]; and can be used in the first hand as well. Responses with tyrosine kinase inhibitors are rapid, with noticeable decreases in the WBC count after 1 to 2 weeks and normalization within 4 to 6 weeks in the majority of patients. The decline in the platelet count is typically delayed by 1 to 2 weeks, with the majority of patients obtaining a CHR within 3 months. Bone marrow morphologies revert to normal in most patients, even patients without cytogenetic responses. Bone marrow cytogenetics should be monitored every 6 months until a complete cytogenetic response is obtained. Quantitative RT-PCR for *BCR-ABL* is a more sensitive assessment of residual disease and may allow earlier detection of relapse. RT-PCR is monitored every 3 to 6 months using marrow or peripheral blood. Based on the PCR levels dosage may need to be escalated.

Because of the risk of myelosuppression, patients should have complete blood counts checked weekly to every other week during the first 2 months of therapy. In the absence of significant myelosuppression, the frequency of hematologic monitoring can then be reduced. But with

myelosuppression, either reducing the dose or stopping the drug should be contemplated. Liver function tests should also be monitored regularly during therapy, as should other laboratory tests to monitor for drug-specific adverse events. [15,16,17] While adverse reactions of gastrointestinal discomfort and edema are shared by all the three drugs; pleural effusion is more with dasatinib and raised liver enzymes and prolonged corrected QT interval with nilotinib and may on occasions require drug interruption.

Because there is no clear end point for when or whether any of these tyrosine kinase inhibitors can be safely discontinued, many pediatric oncologists continue to consider hematopoietic stem cell transplantation in remission. [18, 19]

Cytotoxic agents used in older times include hydroxyurea, interferon alpha with or without cytarabine, and busulfan. These are non curative and their role in Imatinib era is limited to palliation only. They can be of benefit to patients who are not transplantation candidates and are intolerant or refractory to treatment with TKIs.

Conclusion :

CML is a clonal disorder due to balanced translocation t(9;22)(q34;q11) that results in the fusion gene *BCR-ABL*. CML pathobiology shares same features in adult and pediatric age group. Fatigue and splenomegaly are common presentations. Leukocytosis and anaemia with marrow hypercellularity are the usual hematological manifestations of the disease. It is diagnosed in accordance to WHO criteria and divided into chronic, accelerated and blastic-crisis stages. Stem cell transplantation remains the only curative option, though in the era of tyrosine kinase inhibitors, imatinib is the first drug of choice.

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