Chronic myeloid leukemia (CML) is the commonest type of chronic leukemia in India. It has achieved enormous attention in the medical literature because of the delineation of its molecular basis and the discovery of successful targeted therapy in the form of tyrosine kinase inhibitor, imatinib.

Chronic myeloid leukemia is defined as a myeloproliferative disease that originates in an abnormal pleuripotential bone marrow stem cell and is consistently associated with a Philadelphia (ph) chromosome and/or the Bcr-Abl fusion gene. The era of significant discovery started in 1960 when Nowell and Hungerford first observed the occurrence of small chromosome 22 in CML patients (Philadelphia chromosome). In 1980, a reciprocal translocation was identified between chromosome 9 and chromosome 22 that leads to juxtaposition of c-abl oncogene and break point cluster region (BCR). The BCR/ABL gene product has tyrosine kinase activity which is responsible for the initiation and maintenance of malignant transformation of hemopoietic stem cells.

Recent Understanding in Pathogenesis

Recent research has shown that there is a proliferative advantage of Ph positive cells over normal hemopoiesis in the marrow. This is possibly due to the high amount of elastase production by neutrophils. Elastase destroys granulocyte colony stimulating factor (G-CSF) and other hemopoietic growth factors, thus limiting the proliferation of ph negative cells (normal cells) while CML cells continue to proliferate.

BCR/ABL fusion gene products phosphorylate intermediate molecules in three important pathways: proliferation through ras gene activation, maturation through statin activation, and cell adhesion via Crkl gene product. Alteration in these pathways is sufficient to cause the leukemic phenotype. Clonal instability causes progression to accelerated phase and finally to blast transformation.

Clinical Presentations

The classic presentations are fatigue, lassitude, weight loss, and splenomegaly. Occasionally, the diagnosis is made incidentally on blood findings in asymptomatic individuals. Rare presentations are vertigo, priapism, and infections. Presentations like fever, bony pain, chloroma, petechiae and bruising which often indicate accelerated phase or blast transformation.

Diagnosis

The diagnosis of CML is suggested by the high leukocyte count with immature myeloid cells, hypercellular bone marrow and basophilia. Since these features are also shared by other myeloproliferative disorders, the diagnosis of CML is confirmed by chromosomal and molecular analysis.

The leucocyte count varies from slight elevation to even up to 7,00,000/cmm. Platelet count is normal or elevated and there may be normocytic normochronic anemia. There is large number of circulating immature leucocytes (metamyelocytes, myelocytes, blasts). Basophilia is characteristic of CML among myeloproliferative disorders.

Bone marrow aspirate and biopsy reveals hypercellularity. The presence of fibrosis indicates accelerated phase as is the increase in blasts over 15%. Patients with blasts more than 20% are in blast phase.

The typical karyotypic abnormality in CML is t(9:22). An additional chromosomal abnormality or
Philadelphia chromosome duplication indicates disease progression. The fluorescent in situ hybridization (FISH) is a rapid way of detecting the Philadelphia chromosome directly in the blood or bone marrow since it does not rely on dividing cells. About 5% patients are Ph negative on karyotypic analysis. However, half of them have cryptic BCR/ABL transcript detected by southern blot or PCR. Remaining patients are considered to have a form of myelodysplastic syndrome or neutrophilic leukemia. Molecular analysis provides further information on precise transcripts (b2a2, b3a2, e1a2, and e1a3) and also help in detecting residual disease. Neutrophil alkaline phosphatase ([NAP] stain is typically low or absent while serum elastase levels, lactate hydrogenase and vitamin B12 are elevated.

Management

Chronic Phase

With the advent of specific targeted therapy (imatinib), the choice of therapy has now completely changed. Busulphan is now rarely used except in poor patients who can not afford any other therapy. The serious side effect of busulphan is myelo-suppression. Hydroxyurea is used initially for cytoreduction. It does not cause cytogenetic remission hence, does not alter the natural course of the disease. However, majority of CML patients in India receive hydroxyurea as they are not able to afford imatinib. The dose of hydroxyurea is 2-3 gm daily initially followed by smaller dosage in order to maintain leucocyte count around 10,000/cmm. Important side effects are mucositis, hyperpigmentation and leg ulcers.

Imatinib is now considered standard first line therapy in patients with chronic phase CML. The dose is 400 mg daily. The complete hematological response is 98% whereas complete cytogenetic response (CCR) is 84% at 42 months of follow up. The risk of progression to accelerated or blast phase at 42 months is 2%. Imatinib is generally well tolerated. Cytopenia may need reduction in the dose of imatinib. For neutropenia and anemia, growth factor support (G-CSF and EPO) should be considered. Nausea can be minimized if the drug is taken along with a glass of water after meal. Muscle cramp is minimized with calcium supplementation.

What is the Minimum Dose of Imatinib?

It is generally accepted that 300 mg is the minimum dose necessary to achieve plasma concentrations sufficient to inhibit kinase activity of BCR/ABL. The dose of imatinib should preferably not be reduced in the initial 6 months of therapy since early reduction can affect the molecular remission.

Criteria to Predict the Response to Imatinib

Attempts have been made to predict the response to imatinib therapy in patients with CML. Those less likely to respond are advised to opt for allogeneic stem cell transplantation. The assessment can be made before therapy or during the therapy with imatinib.

Pretherapeutic Features

There are various pretherapeutic features which may determine the response to imatinib.

- Sokal score (based on age, spleen size, platelet and peripheral blast count) correlates well with the response to imatinib. The likelihood of achieving complete cytogenetic response (CCR) is 91% in low risk group and 69% in high risk group.
- The early response to therapy is a good indicator of the overall response.
- Presence of additional chromosomal abnormalities (cytogenetic evolution) seems to be an adverse prognostic factor. A higher starting dose (600 mg daily) is recommended in such patients.
- There is no current established role of BCR/ABL mRNA level or Gene Expression Profile (GEP) in predicting the response to imatinib.
- Recently ex vivo assay of phosphorylation of Crkl, myeloid colony formation on imatinib, phosphotyrosine levels in CD34 positive cells, and measurement of BCR/ABL tyrosine phosphorylation, aneuploidy have been shown to correlate with the response to imatinib.
How to Monitor the Response to Imatinib?

It is imperative to monitor the response to imatinib. Patients who show lack of response should be reviewed for the possibilities of other forms of therapy such as allogeneic stem cell transplantation (SCT). The decision should be made early because SCT performed during early phase of the disease gives best results.

The blood count should be done periodically on initiation of imatinib. Generally complete hematological response (CHR) is obtained within 3 months. Patients who do not develop CHR by 3 months should be followed closely as they may need change in the therapy. Achievement of major cytogenetic response (MCR) or CCR at any time during imatinib therapy is associated with prolonged survival. Recent studies suggest that at least a minimal cytogenetic response is desired at 6 months, MCR at 12 months and CCR at 18 months.

Fluorescent in situ hybridization (FISH) is now increasingly used in place of conventional karyotyping. FISH can be done on interphase cells using peripheral blood. While it is more sensitive, it can not detect additional chromosomal abnormalities or CE.

Quantitative PCR (qPCR) is used to detect residual disease in patients with CCR. It can be performed on peripheral blood.

Screening for kinase mutation is generally not recommended before therapy as the prevalence of mutation is very low (0.6%) in stable patients. However, it is performed when there is disease progression or lack of response on imatinib. Mutations such as T315I should be included as these patients will not respond even to alternate kinase inhibitors and are candidates for SCT.

Decision in Patients having Suboptimal Response to Imatinib

Patients who do not show optimal response to imatinib according to the standard monitoring criteria are reviewed for the following options; Patients with low transplant risk should be considered for SCT. For those not a candidate for SCT, dose of imatinib is escalated to 600 mg/day which can give a response in 30%-50% cases. Low dose Ara-C or interferon alpha may be added to imatinib.

Alternative Abl kinase inhibitors like dasatinib or AMN 107 may be tried.

Early Intensification of Therapy

Higher dose imatinib or various combination regimens (with IFNa, Ara-C) have been tried in Phase II studies. Higher dose (600 mg) imatinib have shown greater CCR than standard dose regime (95% vs 76%)\(^\text{10}\). Combination regimens have not shown significantly greater response, however, toxicities were more.

What Happens if Imatinib is Discontinued?

Most patients relapse after discontinuation of imatinib even after they have achieved CCR. However, they respond again to imatinib.

Resistance

The most common mechanism of acquired imatinib resistance is kinase domain mutation in BCR/ABL. To date, more than 40 different mutations have been associated with clinical resistance to imatinib.

Approximately 10% of resistant disease is associated with overproduction of BCR/ABL due to either genomic amplification or acquisition of additional ph chromosome. In some (patient with blast crisis) the resistance occur through mechanisms independent of BCR/ABL such as SRC activation\(^\text{5}\).

Current Status of SCT in CML

The choice of SCT has now changed, although it still remains the only proven curative method of treatment in CML\(^\text{3}\).

In Newly Diagnosed Patients

The option for SCT to young patients with HLA–matched sibling donor should be considered before starting imatinib. The patient should be explained that imatinib does not eradicate leukemia, that life-long therapy is required and that there is a small risk of progression to advanced phase even in those who had achieved excellent response. In most developed countries, almost all patients do now receive imatinib as first line therapy.

In Imatinib Refractory or Resistant Cases

The decision should be individualized. Patients who progress beyond chronic phase on imatinib should be considered for SCT. Although alternative Abl kinase inhibitors show promising activity in such patients\(^\text{11-13}\).

Beyond Imatinib!

Two investigational new small molecule ABL kinase inhibitors have shown efficacy in phase I trial (ASH 2005).
Dasatinib

It is thiazolecarboxamide that is structurally unrelated to imatinib. It has following features;

a. It binds to the ABL kinase domain in active (open) conformation (Imatinib binds to inactive or closed conformation).
b. It also inhibits SRC family kinase.
c. Preclinical studies reveal that it is 300 times more potent than imatinib.
d. It harbor potent inhibitory activity against all (except T315I mutation) imatinib resistant mutants tested.
e. Phase I studies have shown its potent efficacy in imatinib resistant chronic phase disease, accelerated phase and blast crisis.

AMN 107

It is structurally related to imatinib and is 25 times more potent. It does not inhibit SRC kinases. It is ineffective in T315I mutant disease.

Other Agents

Several molecules that can synergize with imatinib in vitro are undergoing evaluation such as inhibitors of RAF, farnesyl transferase, mTOR, and cyclin dependent kinases.

Immunotherapy

Nearly all patients treated with imatinib harbor detectable minimal residual disease. Immunotherapy (such as CMLVX 100, a peptide vaccine) is under trial in order to reduce or eradicate minimal residual disease.

Future Directions

BCR/ABL –T315I mutation presents a major problem. The strategies to overcome resistance mediated by this represents major frontier. A search for such compound is on. Few recently discovered (under study) molecules inhibit BCR/ABL cells by ATP non-competitive fashion. The future treatment of CML may consist of combination therapy including imatinib (or other kinase inhibitors) plus other targeted inhibitors like farnesyl transferase inhibitors and the vaccine.

REFERENCES