## Clinical Presentation

Up to 40% of newly diagnosed CML patients are initially asymptomatic. Other patients exhibit fatigue, lethargy, shortness of breath, weight loss, easy bruising, and early satiety. Physical examination usually detects splenomegaly.

The natural history of CML is characterized by chronic, accelerated, and blastic phases. Patients are typically diagnosed during the chronic phase of CML, an indolent stage lasting 3 to 5 years. Peripheral white blood cell counts are elevated, with eosinophilia and basophilia (>20%) but few blasts (<5%). With control of peripheral blood cell counts, patients are essentially asymptomatic during this period.

Eventually, the disease enters the accelerated phase, which is characterized by fever, weight loss, worsening splenomegaly, and bone pain related to rapid marrow cell turnover. Despite therapy, the white blood cell count rises with increased numbers of circulating blasts (between 10% and 19%). The increased percentage of peripheral blood basophils (>20%) results in histamine production, with symptoms of pruritus, diarrhea, and flushing. During the accelerated phase of CML, patients may develop increasing splenomegaly, persistent thrombocytopenia, or thrombocytosis and leukocytosis, with new clonal cytogenetic abnormalities found in marrow cells.

The CML blast crisis phase marks the evolution to acute leukemia, in which marrow is replaced by 20% or more blasts, with accompanying loss of normal mature cellular elements in the marrow and periphery and extramedullary blast proliferation. Death occurs in a few weeks to months. Two thirds of patients develop AML, whereas the others develop acute lymphocytic (lymphoblastic) leukemia (ALL), a finding confirming that the initial neoplastic cell is an early stem cell capable of multilineage differentiation.

## Treatment

Historically, oral chemotherapeutic agents such as hydroxyurea and busulfan were used to reduce myeloid cell numbers in patients during the chronic phase of CML. Although these drugs decreased the rate of acute disease complications, they did not alter the long-term prognosis or prevent progression to blast crises.

Treatment with interferon resulted in hematologic remissions in 60% to 80% of patients with chronic phase CML and was the first agent to induce cytogenetic responses in 20% to 30% of these patients. Achievement of cytogenetic remissions using interferon-α was associated with prolonged survival, and higher response rates were obtained by combining chemotherapy with interferon. Although most patients treated with interferon still possessed cells with a detectable *BCR/ABL* translocation by PCR and remained at risk for disease relapse, many remained in hematologic and cytogenetic remission for several years. Unfortunately, patients with accelerated or blast crisis CML did poorly with interferon, and high-dose chemotherapy regimens induced only transient responses, with durations of less than 6 months.

Imatinib mesylate (Gleevec, formerly known as STI-571) for the treatment of CML was heralded as the first successful targeted therapy for cancer. Imatinib is a rationally designed competitive inhibitor of multiple tyrosine kinases, including ABL, BCR/ABL, platelet-derived growth factor receptor (PDGFR), and KIT. Inhibition of phosphorylation of BCR/ABL results in blockade of downstream signaling and growth pathways and induces apoptosis of BCR/ABL-positive cells. Preclinical studies demonstrated that imatinib potently inhibited the growth of BCR/ABL-expressing CML cell lines and progenitor cells in vitro and prolonged survival in animal tumor models.

Initial clinical trials of this orally active drug were begun in 1998 in CML patients who had failed interferon-α. Imatinib was well tolerated and had manageable side effects., In the treatment arm, 96% of patients receiving a dose greater than 300 mg per day for 4 weeks achieved hematologic remissions, and 33% obtained cytogenetic remissions after 8 weeks. Imatinib was subsequently shown to be superior to interferon-α and cytarabine in untreated patients with newly diagnosed chronic phase CML and to induce complete cytogenetic responses in almost 90% of patients with chronic phase CML, with an estimated overall survival rate of 89%. Based on this study, imatinib was the first rationally designed biologically targeted drug approved for the treatment of cancer.

Despite these results, imatinib has not cured chronic phase CML. Similar to interferon-α treatment, most patients achieving cytogenetic responses on imatinib demonstrate persistence of BCR/ABL-positive leukemic CML stem cells by sensitive molecular testing. Lifelong imatinib therapy may be required to control disease, and even patients with excellent control of chronic phase CML on imatinib therapy remain at risk for eventual disease progression and therapy failure. It is estimated that up to one third of chronic phase CML patients initiated on imatinib therapy will eventually discontinue drug due to long-term intolerance of drug-induced side effects (e.g., nausea, vomiting, gastrointestinal issues, peripheral and periorbital edema) or development of imatinib resistance.

To address these issues, four newer tyrosine kinase inhibitors (TKIs) of BCR/ABL have been developed for the treatment of chronic phase CML: dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib (Iclusig). All display increased in vitro potency against the BCR/ABL kinase compared with imatinib.

Imatinib, dasatinib, and nilotinib are approved for the initial therapy of chronic phase CML. After the diagnosis, patients are typically started on one of these three TKIs along with careful interim monitoring for toxicities and clinical response. Standardized RT-PCR assays for BCR/ABL are used to measure disease response on a molecular level at 3, 6, and 12 months after therapy initiation. In two randomized clinical trials comparing dasatinib with imatinib or nilotinib with imatinib in newly diagnosed CML patients, both second-generation TKIs outperformed imatinib, as reflected by significantly higher numbers of patients treated with these agents achieving complete cytogenetic and molecular responses at the specific time points compared with imatinib-treated individuals. However, whether these results translate into long-term overall survival benefit for either agent over imatinib remains to be seen.

CML patients resistant to or intolerant of first-line TKI therapy are usually switched to another agent. Up to one half of CML patients who develop resistance to imatinib have cancer cells carrying single-nucleotide mutations in the *BCR/ABL* gene. These mutations result in conformational changes of the BCR/ABL