Chronic myeloid leukemia (CML) accounts for approximately 15% of adult leukemias. Forty percent of patients with CML are asymptomatic, in whom the disease is detected solely based on laboratory abnormalities. Since the introduction of tyrosine kinase inhibitor therapy in 2001, CML has become a chronic disease for the majority of patients. Primary care physicians may be the first to recognize a new diagnosis of CML. In patients with known CML, the primary care physician may be the first to detect disease progression or adverse effects to therapy. This article provides an overview of the clinical presentation, diagnostic approach, and treatment considerations of CML.

Keywords: Leukemia, Myelogenous, Chronic, BCR-ABL Positive; Primary Health Care
INTRODUCTION

Chronic myeloid leukemia (CML) accounts for approximately 15% of adult leukemias, with an estimated 6,660 new cases of CML diagnosed in the United States in 2015. Although the median age of diagnosis is 67 years, CML may present at any age. The advent of tyrosine kinase inhibitor (TKI) therapy has transformed CML from a fatal disease into a chronic disease for the majority of patients. Prior to 1983, the 8-year survival of CML was less than 15%. The 8-year survival improved from 42% to 65% from 1983 to 2000 with the use of interferon-α-based therapy and allogeneic hematopoietic stem cell transplant (HSCT) therapy. With the introduction of TKI therapy in 2001, the 8-year survival is now 87% and continues to improve with the use of second- and third-generation TKI therapy. Given the dramatic decrease in the number of deaths in CML patients and the stable incidence, the prevalence of CML continues to increase. The estimated prevalence of CML in the United States was approximately 70,000 in 2010 and is expected to increase to approximately 112,000 in 2020.

PATHOGENESIS

CML is a clonal myeloproliferative disorder characterized by the presence of a balanced genetic translocation of chromosomes 22 and 9, termed the Philadelphia (Ph) chromosome (Figure 1). The resulting breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion oncogene is translated into the BCR-ABL oncoprotein. BCR-ABL is a constitutively active tyrosine kinase that activates a number of signal-transduction pathways that affect the growth and survival of hematopoietic cells.

CLINICAL MANIFESTATIONS AND STAGING

CML is classified into three different phases: chronic, accelerated, and blast (Table 1). The natural history of CML is a chronic phase for three to five years followed by rapid progression to the fatal blast phase. In two-thirds of patients, the blast phase

![Figure 1. The Philadelphia chromosome. ABL, Abelson murine leukemia; BCR, breakpoint cluster region.](image)

Table 1. Stages of chronic myeloid leukemia

| Phase          | Criteria                                                                 |
|----------------|--------------------------------------------------------------------------|
| Chronic phase  | None of the criteria for accelerated or blast phase are present          |
| Accelerated phase | Blasts ≥ 15% and < 30% in the peripheral blood or bone marrow              |
| MD Anderson Cancer Center and European LeukemiaNet criteria* | Combined blasts and promyelocytes ≥ 30% in the peripheral blood or bone marrow |
| WHO criteria†  | Platelets ≤ 100 × 10^9/L unrelated to therapy                             |
|                | Cytogenetic clonal evolution                                              |
|                | Blasts 10% to 19% in the peripheral blood or bone marrow                  |
|                | Basophilia ≥ 20% in the peripheral blood                                  |
| Blast phase    | Persistent thrombocytopenia (< 100 × 10^9/L) unrelated to therapy         |
| MD Anderson Cancer Center and European LeukemiaNet criteria | Persistent thrombocytosis (> 1,000 × 10^9/L) unresponsive to therapy     |
| WHO criteria   | Increasing spleen size and white blood cell count unresponsive to therapy |
|                | Cytogenetic clonal evolution                                              |

*Most commonly used in clinical trials. †Most commonly used by pathologists.
is proceeded by an accelerated phase. Approximately 85% of patients with CML are diagnosed in the chronic phase.10 Forty percent of patients with chronic phase CML are asymptomatic with the diagnosis made solely based on an abnormal blood count.6 Among the patients who have symptoms, complaints are usually related to anemia and splenomegaly; these include fatigue, weight loss, anorexia, early satiety, and left upper quadrant pain or fullness. Other less common symptoms include thrombosis or bleeding from thrombocytopenia or platelet dysfunction. Splenomegaly is the most common finding on physical exam and is present in over half of patients.11

**DIAGNOSIS**

Unexplained leukocytosis with left shift (immature myeloid cells including myelocytes, promyelocytes or blasts), basophil-ia, and splenomegaly are suggestive of CML (Figure 2). The differential diagnosis includes leukemoid reaction (due to infection or inflammation), Ph negative myeloproliferative disorder, chronic myelomonocytic leukemia, and proliferative myelodysplastic syndrome. On occasion, CML may present as an isolated thrombocytosis. The diagnosis of CML may be confirmed with fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL performed on the peripheral blood. However, bone marrow aspiration with cytogenetic analysis (karyotype) is required to appropriately stage as the chronic phase, accelerated phase, or blast phase and to identify chromosomal abnormalities that are not detectable with FISH for BCR-ABL (Figures 3, 4).12

**TREATMENT**

TKI therapy has transformed the outcomes of patients with CML over the last 15 years. TKIs interfere with the interaction between the BCR-ABL oncoprotein and adenosine triphosphate, thereby blocking proliferation of the malignant clone. There are currently three TKIs approved by the Food and Drug Administration for the first-line treatment of chronic phase CML: imatinib, dasatinib, and nilotinib. Imatinib was the first TKI to be approved in 2001. In the landmark study comparing imatinib to combination interferon and cytarabine therapy, imatinib had superior tolerability, hematologic and cytogenetic responses, and decreased likelihood of progression to accelerated phase or blast phase CML.13 The choice of first-line therapy depends on the Sokal or Hasford risk stratification score, patient age, ability to tolerate therapy, and medical comorbidities. The Sokal score includes age, spleen size, platelet count, and blast percentage.14 The Hasford score also incorporates the percent of eosinophils and basophils.15 Compared to imatinib,
dasatinib and nilotinib have improved efficacy and may be preferred in intermediate- and high-risk patients based on the Sokal or Hasford risk stratification scores.16-19)

In patients who are refractory or intolerant to first-line TKI therapy, second-line options include second-generation TKIs, dasatinib, nilotinib, and bosutinib. Ponatinib is a third-generation TKI and is the only TKI that is effective in patients who harbor the threonine-to-isoleucine mutation at position 315 (T315I). Previously, ponatinib was considered a third-line treatment option. However, due to the associated risk of arterial and venous thromboembolism, its use is generally reserved for patients harboring the T315I mutation.20,21)

All TKI agents are administered orally. The initial dosing and common and notable adverse effects are summarized in Table 2.22,23) The management of toxicities associated with TKI therapy is discussed elsewhere.12,24) Patients with chronic phase CML are continued on TKI therapy indefinitely. Although discontinuation of TKI therapy with close molecular monitoring may be possible in selected patients, the discontinuation of TKI therapy should only be considered in the context of a clinical trial.11,25,26)

The response to therapy is classified based on hematological, cytogenetic, and molecular responses (Table 3).12) Optimal responses to first-line TKI therapy include complete hematologic response with BCR-ABL1 transcript < 10% (RT-PCR) and/or Ph positive cells ≤ 35% (bone marrow cytogenetics) at 3 months, BCR-ABL1 transcript < 1% and/or no detectable Ph positive cells at 6 months, and BCR-ABL1 transcript ≤ 0.1% at 12 months. Failure of first-line TKI therapy is defined as failure to achieve a complete hematologic response and/or Ph positive cells > 95% at 3 months, BCR-ABL1 transcript > 10% and/or Ph positive cells > 35% at 6 months, and BCR-ABL1 transcript > 1%

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Table 2. Tyrosine kinase inhibitors available for treatment of chronic phase chronic myeloid leukemia

| Tyrosine kinase inhibitors | First-line treatment | Second-line and subsequent therapy | Recommended dose | Common adverse effects (≥ 10% of patients) | Notable adverse events |
|---------------------------|----------------------|------------------------------------|------------------|-------------------------------------------|-----------------------|
| Imatinib (Gleevec)        | Yes                  | No                                 | 400 mg orally once daily; take with food | Myelosuppression, fatigue, insomnia, depression, dizziness, fluid retention, weight gain, upper respiratory tract infection, influenza, pyrexia, cough, abdominal pain, nausea, vomiting, diarrhea, myalgia, arthralgia, skin rash, hemorrhage | Rarely associated with appendiceal carcinoma25) |
| Dasatinib (Sprycel)       | Yes                  | Yes                                | 100 mg orally once daily | Myelosuppression, fatigue, fluid retention, headache, dyspnea, infection, abdominal pain, nausea, diarrhea, myalgia, arthralgia, skin rash, hemorrhage | Pleural effusion |
| Nilotinib (Tasigna)       | Yes                  | Yes                                | 300 mg orally twice daily for first-line therapy, 400 mg orally for refractory disease; take on an empty stomach | Myelosuppression, fatigue, headache, nausea, vomiting, diarrhea, constipation, skin rash, pruritis | QT interval prolongation |
| Bosutinib (Bosulif)       | No                   | Yes                                | 500 mg once daily; take with food | Myelosuppression, fatigue, headache, dyspnea, cough, pyrexia, abdominal pain, nausea, vomiting, diarrhea, constipation, increased aspartate aminotransferase/ALT, arthralgia, skin rash | |
| Ponatinib (Iclusig)       | No                   | Yes; for the patients with the T315I mutation | 45 mg once daily | Myelosuppression, fatigue, headache, hypertension, dyspnea, pyrexia, abdominal pain, pancreatitis, nausea, constipation, increased ALT, myalgia, arthralgia, skin rash, dry skin | Arterial and venous thrombosis Hepatotoxicity, liver failure and death24) |

ALT, alanine aminotransferase.

Table 3. Assessment response to tyrosine kinase inhibitor therapy

| Content | |
|---------|---------|
| Complete hematologic response | Normalization of leukocyte count (white blood cell count < 10 cells × 10^9/L) and platelet count (platelets < 10 cells × 10^10/L), no immature cells or blasts in the peripheral blood, no signs or symptoms of disease with the disappearance of palpable splenomegaly |
| Cytogenetic response | % Philadelphia chromosome positive metaphases: (with a minimum of 20 metaphases examined) |
| Minor: 35%–90% | Partial: 1%–34% |
| Major: 0%–35% (complete+partial) | Complete: 0% |
| Molecular response | Major: ≥ 3 log reduction of BCR-ABL1 mRNA expression |
| Complete: BCR-ABL1 mRNA expression undetectable by reverse-transcriptase polymerase chain reaction |
| Relapse | Loss of hematologic or cytogenetic response |
| BCR, breakpoint cluster region; ABL, Abelson murine leukemia; mRNA, messenger ribonucleic acid. |
and/or Ph positive cells at 12 months. Loss of complete hematologic response, complete cytogenetic response, or major molecular response or presence of mutations or clonal evolution are also considered as treatment failure.\(^6\)

Administration of the protein synthesis inhibitor omacetaxine is a treatment option for patients who have failure or intolerance to two or more TKIs, including patients who harbor the T315I mutation.\(^{27,28}\) The accelerated or blast phases may be treated with an alternative TKI as a bridge to HSCT. HSCT is a potentially curative treatment in patients with CML, and HSCT evaluation is recommended for patients with the T315I mutation, failure or intolerance to two or more TKIs, or those with accelerated or blast phase CML.\(^{12}\)

**PREGNANCY**

Although most pregnancy outcomes are normal in patients exposed to imatinib, there is still a risk for serious fetal malformation with imatinib exposure.\(^{29}\) For this reason, discontinuation of TKI therapy is generally advised during pregnancy. For women who desire pregnancy, a planned pregnancy is preferred. Once a woman is in at least a major molecular response, then a two to three month washout period of TKI therapy is advised prior to conception. TKI therapy should be held during pregnancy and resumed immediately after birth. When treatment is needed during pregnancy due to a very high white blood cell (WBC) count, leukapheresis is preferred.\(^{30}\) Interferon may be used safely in pregnancy. However, its use is limited by toxicity and slow time to response.\(^{31-33}\) The use of hydroxyurea also appears to be safe in pregnancy, but its use is typically reserved for pulse dosing to control very high WBC counts.\(^{36,34-39}\)

Although the use of TKI appears to be safe in men fathering a child, patients should be advised that the data in this setting is limited.\(^{40-42}\)

**ROLE OF THE PRIMARY CARE PHYSICIAN**

Primary care physicians may be the first to detect CML since 40% patients present only with an abnormal blood count.\(^5\) Thus, it is important for primary care physicians to be aware of the appropriate initial evaluation of patients with suspected CML.

During the routine follow-up of other medical comorbidities, the primary care physician may be the first to detect new adverse effects to TKI therapy, treatment failure, or progression of disease. With recognition of the common and serious adverse effects of TKI therapy, the primary care physician may provide appropriate counseling or arrange for earlier follow-up with the patient’s hematologist/oncologist for management. With the recognition of possible treatment failure or progression of disease from the chronic phase to the accelerated or blast phases (i.e., increasing WBC count), the primary care physician should arrange for the patient to be seen by his/her hematologist/oncologist promptly for further evaluation.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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