Among patients developing resistance to TKIs, several resistance mechanisms have been observed. The most clinically relevant one is the development of different *ABL1* kinase domain mutations that prevent the binding of TKIs to the catalytic site (ATP binding site) of the kinase. More than 100 *BCR-ABL1* mutations have now been described, many of which confer relative or absolute resistance to imatinib. This has resulted in the development of second-generation TKIs (i.e., dasatinib, nilotinib, bosutinib) and of a third-generation TKI (ponatinib) with selective efficacy against T315I, a mutation of the gatekeeper residue of the kinase that causes resistance to all other TKIs.

CLINICAL PRESENTATION

The presenting signs and symptoms in CML depend on the availability of and access to health care procedures, including physical exams and screening tests. In the United States, because of the easy access to health care screening and physical exams, 50–60% of patients are diagnosed on routine blood tests and have minimal symptoms at presentation, such as fatigue. In geographic locations where access to health care is more limited, patients often present with high CML burden including splenomegaly, anemia, and related symptoms (abdominal pain, weight loss, fatigue), as well as a higher frequency of high-risk CML. Presenting findings in patients diagnosed in the United States are shown in Table 133-1.

Symptoms Most patients with CML (90%) present in the indolent or chronic phase. Depending on the timing of diagnosis, patients are often asymptomatic (if the diagnosis is discovered during health care screening tests). Common symptoms, when present, are manifestations of anemia and splenomegaly. These may include fatigue, malaise, weight loss (if high leukemia burden), or early satiety and left upper quadrant pain or masses (from splenomegaly). Less common presenting findings include thrombotic or vasoocclusive events (from severe leukocytosis or thrombocytosis). These include priapism, cardiovascular complications, myocardial infarction, venous thrombosis, visual disturbances, dyspnea and pulmonary insufficiency, drowsiness, loss of coordination, confusion, or cerebrovascular accidents. Bleeding diatheses findings include retinal hemorrhages, gastrointestinal bleeding, and others. Patients who present with, or progress to, the accelerated or blastic phases have additional symptoms including unexplained fever, significant weight loss, severe fatigue, bone and joint aches, bleeding and thrombotic events, and infections.

TABLE 133-1 PRESENTING SIGNS AND SYMPTOMS OF NEWLY DIAGNOSED PHILADELPHIA CHROMOSOME–POSITIVE CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE

Parameter	Percentage
Age ≥60 years (median)	18 (46)
Female gender	35–45
Splenomegaly	30
Hepatomegaly	5
Lymphadenopathy	5
Other extramedullary disease	2
Hemoglobin <10 g/dL	10–15
Platelets	
>450 × 10^9 cells/L	30–35
<100 × 10^9 cells/L	3–5
White blood cells ≥50 × 10^9 cells/L	35–40
Marrow	
≥5% blasts	5
≥5% basophils	10–15
Peripheral blood	
≥3% blasts	8–10
≥7% basophils	10
Cytogenetic clonal evolution other than the Philadelphia chromosome	4–5
Sokal risk	
Low	60–65
Intermediate	25–30
High	10

Physical Findings Splenomegaly is the most common physical finding, occurring in 20–70% of patients depending on health care screening frequency. Other less common findings include hepatomegaly (10–20%), lymphadenopathy (5–10%), and extramedullary disease (skin or subcutaneous lesions). The latter indicates CML transformation if a biopsy confirms the presence of sheets of blasts. Other physical findings are manifestations of complications of high tumor burden described earlier (e.g., cardiovascular, cerebrovascular, bleeding). High basophil counts may be associated with histamine overproduction causing pruritus, diarrhea, flushing, and even gastrointestinal ulcers.

Hematologic and Marrow Findings In untreated CML, leukocytosis ranging from 10–500 × 10^9/L is common. The peripheral blood differential shows left-shifted hematopoiesis with predominance of neutrophils and the presence of bands, myelocytes, metamyelocytes, promyelocytes, and blasts (usually ≤5%). Basophils and/or eosinophils are frequently increased. Thrombocytosis is common, but thrombocytopenia is rare and, when present, suggests a worse prognosis, disease acceleration, or an unrelated etiology. Anemia is present in one-third of patients. Cyclic oscillations of counts are noted in 25% of patients without treatment. Biochemical abnormalities include a low leukocyte alkaline phosphatase score and high levels of vitamin B_{12}, uric acid, lactic dehydrogenase, and lysozyme. The presence of unexplained and sustained leukocytosis, with or without splenomegaly, should lead to a marrow examination and cytogenetic analysis.

The bone marrow is hypercellular with marked myeloid hyperplasia and a high myeloid-to-erythroid ratio of 15–20:1. Marrow blasts are 5% or less; when higher, they carry a worse prognosis or represent acceleration (if they are ≥15%). Increased reticulin fibrosis (by Snook's silver stain) is common, with 30–40% of patients demonstrating grade 3–4 reticulin fibrosis. This was considered adverse in the pre-TKI era. With TKI therapy, reticulin fibrosis resolves in most patients and is not an indicator of poor prognosis. Collagen fibrosis (Wright-Giemsa stain) is rare at diagnosis. Disease progression with a "spent phase" of myelofibrosis (myelophthisis, or burnt-out marrow) was common with busulfan therapy (20–30%) but is rare with TKI therapy.

Cytogenetic and Molecular Findings The diagnosis of CML is straightforward and depends on documenting t(9;22)(q34;q11.2), which is found in 90% of cases. This is known as the Philadelphia-chromosome abnormality (discovered in Philadelphia) and was initially identified as a shortened chromosome, later identified to be chromosome 22 (22q–) (Fig. 133-1). Some patients may have complex translocations (variant Ph) involving three or more translocations that include chromosomes 9 and 22 and one or more other chromosomes. Others may have a "masked Ph," involving translocations between chromosome 9 and a chromosome other than 22. The prognosis of these patients and their response to TKI therapy are similar to those in patients with Ph. About 5–10% of patients may have additional chromosomal abnormalities in the Ph-positive cells. These usually involve trisomy 8, a double Ph, isochromosome 17 or 17p deletion, 20q–, or others. This is referred to as clonal evolution and was historically a sign of adverse prognosis, particularly when trisomy 8, double Ph, or chromosome 17 abnormalities were noted.

Techniques such as FISH and PCR are now used to aid in the diagnosis of CML. They are more sensitive approaches to estimate the CML burden in patients on TKI therapy. They can be done on peripheral samples, and thus are less painful and more convenient. Patients with CML at diagnosis should have a FISH analysis to quantify the percentage of Ph-positive cells, if FISH is used to replace marrow cytogenetic analysis in monitoring response to therapy. FISH may not detect additional chromosomal abnormalities (clonal evolution); thus, a cytogenetic analysis is usually recommended at the time of diagnosis. The *BCR-ABL1* RNA message is usually one of two variants: e13a2 (formerly b2a2) and e14a2 (formerly b3a2). About 2–5% of patients