

Clinical manifestations and diagnosis of chronic myeloid leukemia

AUTHOR: Richard A Van Etten, MD, PhD

SECTION EDITOR: Richard A Larson, MD

DEPUTY EDITOR: Alan G Rosmarin, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Aug 2023**.

This topic last updated: **May 31, 2022**.

INTRODUCTION

Chronic myeloid leukemia (CML; also known as chronic myelocytic, chronic myelogenous, or chronic granulocytic leukemia) is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation. (See "Overview of the myeloproliferative neoplasms".)

CML is associated with the fusion of two genes: *BCR* (on chromosome 22) and *ABL1* (on chromosome 9) resulting in the *BCR::ABL1* fusion gene. This abnormal fusion typically results from a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11), that gives rise to an abnormal chromosome 22 called the Philadelphia (Ph) chromosome. It is this derivative chromosome 22 that harbors the *BCR::ABL1* fusion gene.

The *BCR::ABL1* fusion gene results in the formation of a unique gene product, the *BCR::ABL1* fusion protein. This protein product includes an enzymatic domain from the normal *ABL1* with tyrosine kinase catalytic activity, but relative to *ABL1*, whose kinase activity is tightly regulated [1], the kinase activity of *BCR::ABL1* is elevated and constitutive [2] due to fusion with a portion of *BCR*. It is this deregulated tyrosine kinase that is implicated in the pathogenesis of CML. (See "Molecular genetics of chronic myeloid leukemia".)

The clinical hallmark of CML is the uncontrolled production of mature and maturing granulocytes, predominantly neutrophils, but also basophils and eosinophils. In the absence of

treatment, CML has a triphasic or biphasic clinical course as it progresses from a chronic phase to an accelerated phase and on to a terminal blast crisis. Sometimes it goes from chronic phase directly to blast crisis, particularly when the blast phase is lymphoid.

The clinical manifestations and diagnosis of CML will be reviewed here. The molecular genetics, biology, and treatment of this disorder are considered separately. (See "Molecular genetics of chronic myeloid leukemia" and "Cellular and molecular biology of chronic myeloid leukemia" and "Overview of the treatment of chronic myeloid leukemia".)

EPIDEMIOLOGY

CML accounts for approximately 15 to 20 percent of leukemias in adults [3]. It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance [4-6]. The median age at presentation is approximately 50 years for patients enrolled on clinical studies, but the actual median age from cancer registry data may be 10 years older. Exposure to ionizing radiation is the only known risk factor [7,8].

While there is no known familial disposition to CML [9], rare families in which multiple members develop myeloproliferative neoplasms (MPNs), including CML, have been described [10]. Studies of these families suggest the presence of an autosomal dominant mutation that may predispose to acquisition of a secondary somatic mutation such as the Philadelphia chromosome translocation or *JAK2* mutation. It is unknown whether specific genetic variants predispose persons in the general population to develop CML. However, a genome-wide association study of Korean and European cohorts suggested that persons with genetic variants at two chromosomal loci, 6q25.1 and 17p11.1, may be more likely to develop CML [11]. (See "Molecular pathogenesis of congenital erythrocytoses and polycythemia vera", section on 'Familial PV'.)

The prevalence of CML is steadily increasing in the Western world, due to the dramatic effect of ABL1 kinase inhibitors on survival. It is estimated that there will be >180,000 patients living with CML in the United States by the year 2050 [12].

CLINICAL MANIFESTATIONS

CML has a triphasic or biphasic clinical course: a chronic phase, which is present at the time of diagnosis in approximately 85 percent of patients; an accelerated phase, in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with treatment; and blast crisis, a condition resembling acute leukemia in which myeloid

or lymphoid blasts proliferate in an uncontrolled manner [7]. The varying definitions of these disease phases are discussed in more detail separately. (See "Overview of the treatment of chronic myeloid leukemia", section on 'Pretreatment evaluation'.)

The clinical findings at diagnosis of CML vary among reported series and also depend on the stage of disease at diagnosis. Twenty to 50 percent of patients are asymptomatic, with the disease first being suspected from routine blood tests [7,13]. Among symptomatic patients, systemic symptoms such as fatigue (34 percent), malaise (3 percent), weight loss (20 percent), excessive sweating (15 percent), abdominal fullness (15 percent), and bleeding episodes due to platelet dysfunction (21 percent) are common [13].

Abdominal pain and discomfort may include left upper quadrant pain (sometimes referred to the left shoulder) and early satiety, due to the enlarged spleen with or without perisplenitis and/or splenic infarction. Tenderness over the lower sternum, due to an expanding bone marrow, is sometimes seen. Acute gouty arthritis may also present at this time, due to overproduction of uric acid. (See "Asymptomatic hyperuricemia".)

Other frequent findings include splenomegaly (present in 48 and 76 percent in two series), anemia (45 and 62 percent), white blood cell count above 100,000/microL (52 and 72 percent), and platelet count above 600,000 to 700,000/microL (15 and 34 percent) [7,13]. Involvement of extramedullary tissues such as the lymph nodes, skin, and soft tissues is generally limited to patients with blast crisis.

PATHOLOGIC FEATURES

Peripheral blood — The peripheral smear typically demonstrates leukocytosis with a median white count of approximately 100,000/microL (range 12,000 to 1,000,000/microL) [14]. The white blood cell differential typically shows virtually all cells of the neutrophilic series, from myeloblasts to mature neutrophils with peaks in the percent myelocytes and segmented neutrophils (picture 1). Blasts typically account for less than 2 percent. The presence of a greater percent of myelocytes than the more mature metamyelocytes ("leukemic hiatus" or "myelocyte bulge") is one of the classic findings in CML [15]. The granulocytes of chronic phase are morphologically normal with no evidence of dysplasia, but dysplasia can develop in more advanced disease, and particularly in accelerated phase. (See "Evaluation of the peripheral blood smear", section on 'Neutrophil series'.)

Although morphologically normal, the neutrophils in CML are cytochemically abnormal. The cytochemical reaction called leukocyte (or neutrophil) alkaline phosphatase (LAP, or NAP) when

scored is low. The low LAP score is useful in excluding a reactive leukocytosis or "leukemoid reaction," typically due to infection, in which the score is typically elevated or normal. Low LAP activity was also classically used to exclude polycythemia vera (PV) in the differential diagnosis of CML, in which LAP activity is also often increased. (See "Clinical manifestations and diagnosis of polycythemia vera".)

Absolute basophilia is a universal finding in the blood smears from CML patients, and absolute eosinophilia is seen in about 90 percent of cases. Absolute moncytosis ($>1000/\text{microL}$) is not uncommon, although the percentage of monocytes is typically low (<3 percent). The occasional patients with CML who have an alternate breakpoint in chromosome 22, producing a p190 BCR::ABL1 fusion protein rather than the classic p210 BCR::ABL1 fusion protein, tend to have a more prominent moncytosis and a low neutrophil/monocyte ratio in the peripheral blood [16,17]. (See "Cellular and molecular biology of chronic myeloid leukemia", section on 'BCR-ABL1'.)

The platelet count can be normal or elevated. Platelet counts above 600,000/ μL are seen in 15 to 30 percent of patients [7,13]. Low platelet counts or thrombocytopenia, if present at diagnosis, should make one reconsider other diagnostic possibilities, such as one of the myelodysplastic syndromes. A normochromic, normocytic anemia is seen in 45 to 60 percent of patients.

Bone marrow biopsy — Bone marrow aspiration and biopsy demonstrates granulocytic hyperplasia with a maturation pattern that reflects that seen in the peripheral smear (picture 2). Other non-specific bone marrow findings include an increase in reticulin fibrosis and vascularity. (See "Overview of angiogenesis inhibitors", section on 'Vascular endothelial growth factor').

There is usually a thicker layer of immature neutrophils in the paratrabecular cuff and mature neutrophils are found in the intertrabecular areas. Erythroid islands are reduced in number and size. Small megakaryocytes with hypolobulated nuclei (so-called "dwarf megakaryocytes") are present. These are smaller than normal megakaryocytes, but not as small as dysplastic "micromegakaryocytes." Markers of increased cell turnover are commonly noted with Pseudo-Gaucher cells and sea-blue histiocytes. Iron-laden macrophages are reduced or absent.

The peripheral blood and bone marrow aspirate differential count are key components of determining the disease stage. In general, peripheral blood and bone marrow blasts between 10 and 19 percent are diagnostic of accelerated phase disease, while blasts over 20 percent are diagnostic of blast crisis. Additional criteria for accelerated phase are also described, and these

are discussed in more detail separately. (See "Overview of the treatment of chronic myeloid leukemia", section on 'Pretreatment evaluation'.)

Genetics — Genetic testing for the Philadelphia chromosome (figure 1), the BCR::ABL1 fusion gene (figure 2) or the fusion mRNA gene product is done by conventional cytogenetic analysis (karyotyping), fluorescence in situ hybridization (FISH) analysis, or by reverse transcription polymerase chain reaction (RT-PCR). Southern blot techniques to identify *BCR::ABL1* gene rearrangements were used in the past, but are time consuming and no longer employed as a routine diagnostic test. Evaluating for BCR::ABL1 protein by Western blot analysis is also not typically done. All patients with CML have evidence of the Philadelphia chromosome (Ph) (figure 1), the *BCR::ABL1* fusion gene or its product, the *BCR::ABL1* fusion mRNA (figure 2) by at least one of these tests [14].

The vast majority of patients (90 to 95 percent) demonstrate the t(9;22)(q34;q11.2) reciprocal translocation that results in the Ph chromosome. Some of the remaining minority have variant translocations such as complex translocations involving other chromosome (eg, t(9;14;22)). The rest have cryptic translocations of 9q34 and 22q11.2 that cannot be identified by routine cytogenetics. These are referred to as "Ph-negative" and require FISH analysis to identify the *BCR::ABL1* fusion gene, or RT-PCR to identify the *BCR::ABL1* fusion mRNA.

As an example, approximately 15 percent of patients in a large prospective study lacked the Ph chromosome by cytogenetic analysis [13]. However, about one-half of such patients had complex chromosomal rearrangements masking a t(9;22) translocation; another subset was Ph-negative by karyotype but had evidence of *BCR::ABL1* gene fusion by metaphase or interphase FISH analysis or RT-PCR. The clinical features of both groups of these patients are very similar to those with typical Ph chromosome-positive CML. In contrast, patients whose cells lack evidence of *BCR::ABL1* gene fusion by FISH or RT-PCR do not have CML, but may have a related condition, such as a myelodysplastic syndrome or disease with overlapping MDS/MPN features. (See 'Differential diagnosis' below.)

There are several distinct BCR::ABL1 fusion proteins generated from the chromosomal translocation or molecular fusion, depending on the site of the breakpoint in the BCR gene on chromosome 22.

- The most common abnormal *BCR::ABL1* fusion transcript produced is from a breakpoint in exon 13 or exon 14 (alternatively called exon b2 or b3) in the *BCR* gene, fused to the *ABL1* gene at exon a2. These are referred to as e13a2, e14a2 or alternatively as b2a2 or b3a2. These fusions result in a BCR::ABL1 protein with 210 kilodalton molecular mass which is

referred to as the p210 BCR::ABL1 protein. This p210 BCR::ABL1 protein has increased and constitutively activated tyrosine kinase activity, as discussed above.

- Less commonly, an alternative e19a2 fusion transcript is found, producing a larger fusion protein with 230 kilodalton weight (p230 BCR::ABL1). This is seen in rare CML cases (<1 percent).
- A smaller e1a2 fusion transcript, which produces the p190 BCR::ABL1 protein is also seen in a very small number of CML patients, but is more frequently associated with Ph-positive acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL). It is also often produced in small quantities by patients with the classic p210 transcript as a form of alternative splicing of the BCR gene.
- In addition, rare patients with fusion of *BCR* exon 1 or exon b2 to *ABL1* exon 3 (e1a3 and b2a3) and *BCR* exon 6 to *ABL1* exon 2 (e6a2) have been described.

Common RT-PCR assays available in most commercial and academic laboratories will only detect the p210 and p190 variants of BCR::ABL1. If patients with suspected CML are negative for *BCR::ABL1* transcripts by RT-PCR, it is important to exclude the possibility of *BCR::ABL1* gene fusion by FISH.

All the BCR::ABL1 fusion proteins exhibit dysregulated tyrosine kinase activity. (See "Molecular genetics of chronic myeloid leukemia", section on 'Distinct forms of BCR-ABL1 from alternative chromosome 22 breakpoints' and "Cellular and molecular biology of chronic myeloid leukemia", section on 'The BCR-ABL1 fusion protein'.)

Although the Ph chromosome translocation is the initiating event in CML, progression to accelerated phase or blast crisis appears to require the acquisition of other chromosomal or molecular changes [7]. Additional cytogenetic abnormalities develop in over 80 percent of patients in the accelerated and blast crisis phases, most commonly trisomy 8, trisomy 19, duplication of the Ph chromosome, and isochromosome 17q (leading to the loss of the P53 gene on 17p). These can be seen singly in addition to the Ph chromosome or in any combination. The acquisition of any of these additional karyotypic findings confers a worse prognosis [18]. These additional cytogenetic aberrations may also be found at the time of diagnosis in approximately 7 percent of patients and are associated with a lower response rate to tyrosine kinase inhibitors and inferior survival [19,20]. (See "Cellular and molecular biology of chronic myeloid leukemia", section on 'Progression to acute phase CML'.)

DIAGNOSIS

The diagnosis of CML is first suspected by identifying the typical findings in the blood and bone marrow, and then confirmed by the demonstration of the Philadelphia chromosome (figure 1), the *BCR::ABL1* fusion gene or the *BCR::ABL1* fusion mRNA (figure 2) by conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR) [14,21]. (See 'Differential diagnosis' below and "Molecular genetics of chronic myeloid leukemia".)

Hydroxyurea can be used to reduce white blood cell counts while awaiting confirmation of a suspected diagnosis of CML in a patient with significant leukocytosis (eg, $>80 \times 10^9$ white cells/L). (See "Overview of the treatment of chronic myeloid leukemia", section on 'Other agents'.)

DIFFERENTIAL DIAGNOSIS

There are several other disorders that resemble CML clinically. These include a leukemoid reaction, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, "atypical CML," chronic eosinophilic leukemia, chronic neutrophilic leukemia, other myeloproliferative neoplasms, and other Philadelphia chromosome (Ph)-positive leukemias. These are discussed below:

Leukemoid reaction — A leukemoid reaction describes a high leukocyte count with neutrophilia and prominent left shift, usually in response to infection. The peripheral blood count may be as high as 50,000/microL and can easily mimic CML. However, the following features are more commonly found in a leukemoid reaction and help to distinguish it from CML: toxic granulation in the neutrophils, a high LAP score, lack of a "myelocyte bulge," and most importantly, the presence of an obvious cause for the neutrophilia. Bone marrow examination is often not helpful. Cytogenetic or molecular testing is definitive for CML if the distinction cannot be made clinically.

Juvenile myelomonocytic leukemia — Juvenile myelomonocytic leukemia (JMML, formerly called "juvenile CML") is a rare fatal disorder of infancy and early childhood characterized by the combination of hepatosplenomegaly, lymphadenopathy, pallor, fever, and skin rash (table 1) [22-24].

Patients with JMML demonstrate clonal overproduction of maturing myeloid cells, usually with an excess of monocytic lineage cells that are hyper-responsive to granulocyte macrophage colony-stimulating factor (GM-CSF), leading to organ infiltration with relatively normal-appearing monocytes and macrophages and death from organ failure or infection [25,26]. In contrast to CML, the karyotype in JMML is normal or sometimes shows monosomy 7, and

progression to acute leukemia is rare. Many patients with JMML have mutations in genes that encode elements of the GM-CSF signal transduction pathway, including *PTPN11*, *NRAS* and *KRAS2*, *CBL*, and *NF1* [27-30]. (See "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)", section on 'Epidemiology'.)

It is notable that children and infants can have typical CML. Because of the imprecise older term "juvenile CML" for JMML, it is important to clearly indicate if the case is truly CML by noting that it is "*BCR::ABL1* positive or Ph positive." The correct diagnosis will have important treatment implications and must be communicated unambiguously.

Chronic myelomonocytic leukemia — Chronic myelomonocytic leukemia (CMML) is a myelodysplastic/myeloproliferative neoplasm characterized by the overproduction of maturing monocytic cells and sometimes dysplastic neutrophils, often accompanied by anemia and/or thrombocytopenia [31]. Unlike CML, the bone marrow morphology in CMML demonstrates prominent dysplastic changes in at least two of the three myeloid lineages. In addition, genetic testing does not demonstrate evidence of *BCR::ABL1*, the Ph chromosome or their products. (See "Chronic myelomonocytic leukemia: Clinical features, evaluation, and diagnosis", section on 'Diagnosis').

"Atypical CML" — "Atypical CML" is a myelodysplastic/myeloproliferative neoplasm that is characterized by features of dysplasia and of myeloid proliferation at the same time. The entity is uncommon, but can cause a considerable diagnostic challenge. Patients are elderly and present with high neutrophil counts but with thrombocytopenia and/or anemia. The bone marrow shows increased cellularity due to a granulocytic proliferation without increased blasts. There is no moncytosis in the blood or marrow. The distinguishing feature of "atypical CML" is the presence of dysplasia in the neutrophils, and sometimes in the megakaryocytes and erythroid forms as well (table 2) [21,32,33].

"Atypical CML" is an unfortunate term for this disorder since it is **not** a type of CML that is "atypical." It is *BCR::ABL1* negative and Ph negative, a finding that should be noted in the diagnosis to avoid confusion. Atypical CML can be associated with other cytogenetic changes including trisomy 8, and isochromosome 17q [34]. In one study, recurrent somatic point mutations of set-binding protein 1 (*SETBP1*) were identified in 17 of 70 (24 percent) cases of atypical CML; a smaller percentage of cases of myelodysplastic syndrome/myeloproliferative disorder, chronic myelomonocytic leukemia, and chronic neutrophilic leukemia; and none of 458 individuals with other hematologic malignancies [35]. In another study, activating point mutations in the colony stimulating factor 3 receptor (*CSF3R*) gene were identified in 8 of 18 patients with atypical CML and 8 of 9 patients with chronic neutrophilic leukemia, but only 4 of 344 patients with other leukemias [36]. (See 'Chronic neutrophilic leukemia' below.)

The prognosis of patients with atypical CML is poor, and transformation to acute myeloid leukemia (AML) can occur [37].

Chronic eosinophilic leukemia — Chronic eosinophilic leukemia (CEL) is a rare clonal chronic myeloproliferative disorder characterized by the overproduction of normal-appearing eosinophils in the bone marrow with proliferation in the blood and infiltration into the organs resulting in end-organ damage (table 3). There is only a minor tendency to progress to AML [38].

Cytogenetics in CEL may be normal or exhibit clonal abnormalities including del(4q12), rearrangement of 5q22, 12p12-133, or 8p11. Molecularly, some cases have rearrangements involving the tyrosine kinases *PDGFRA*, *PDGFRB*, *FGFR1*, or *JAK2* [21,39,40]. Cases of CEL do not demonstrate the Ph chromosome or *BCR::ABL1* gene fusion. However, some cases do respond to imatinib therapy since the underlying molecular pathogenesis is related to overactivity of an imatinib-sensitive tyrosine kinase. (See "Hypereosinophilic syndromes: Clinical manifestations, pathophysiology, and diagnosis", section on 'Diagnosis of myeloproliferative variants'.)

Chronic neutrophilic leukemia — Chronic neutrophilic leukemia (CNL) is a rare disorder characterized by mature granulocytic proliferation in the blood and marrow, and infiltration into the organs resulting in hepatosplenomegaly. There is often toxic granulation in the neutrophils, nuclear hypersegmentation and an increased leukocyte alkaline phosphatase (LAP) score (table 4) [33,41-44]. The Ph chromosome and its products are not detected in patients with chronic neutrophilic leukemia. Although these patients do not usually progress to AML, their survival is short and usually less than two years. Effective treatment is uncertain; some patients have responded to interferon [41] and the JAK1/2 inhibitor ruxolitinib [36].

A subset of patients with CNL demonstrates point mutations in the *CSF3R* gene, which encodes the receptor for CSF3 (previously called G-CSF), an integral part of the regulation of neutrophil production in both steady-state and in response to stress [36,45,46]. In one study, activating point mutations of *CSF3R* were identified in 8 of 9 patients with CNL and 8 of 18 patients with atypical CML, but only 4 of 344 patients with other leukemias [36]. Further analysis demonstrated two classes of mutations: point mutations involving the juxtamembrane regions, and nonsense or frameshift mutations resulting in truncation of the COOH-terminal cytoplasmic tail of *CSF3R*. Biochemical studies showed cells carrying *CSF3R* truncation mutations were sensitive to the multikinase inhibitor dasatinib, while those carrying membrane proximal mutations were sensitive to the JAK inhibitor ruxolitinib. A patient with a *CSF3* proximal membrane mutation demonstrated a dramatic response following treatment with ruxolitinib. Together, these findings suggest that mutations in *CSF3* have a central role in the pathogenesis

of some patients with CNL or atypical CML. Further studies are needed to evaluate the use of tyrosine kinase inhibitors in patients with *CSF3R* mutations.

It is notable that some patients with myeloma or other immunoproliferative disease with increased plasma cells can have marked neutrophilia. This may be due to the secretion of neutrophil-stimulating cytokines from the plasma cells. Such cases likely represent reactive neutrophilia and not CNL. True cases of CNL should have clonal neutrophils that might be demonstrated by a cytogenetic clone or by clonality studies such as the HUMARA analysis. Rare cases of CML have a p230 BCR::ABL1, and these may be associated with either a prominent neutrophil proliferation or a prominent thrombocytosis. The former (sometime referred to as "CML-N") may be particularly difficult to distinguish from CNL.

Other myeloproliferative neoplasms — A small number of patients present with clinical characteristics of one of the other myeloproliferative neoplasms (eg, essential thrombocythemia or polycythemia vera) but are Ph-positive by cytogenetic analysis. The majority of these patients exhibits a clinical course consistent with CML, including eventual progression to blast crisis, and must be considered CML with an atypical initial presentation [47]. The typical non-CML myeloproliferative neoplasms (polycythemia vera, essential thrombocytosis, and primary myelofibrosis) are *BCR::ABL1* negative and Ph chromosome negative, and will not respond to imatinib therapy.

Sensitive reverse transcriptase-polymerase chain reaction (RT-PCR) assays for detection of the *BCR::ABL1* fusion mRNA have shown that this product can be detected at low levels in approximately 50 percent of Ph-negative patients with essential thrombocythemia; these individuals do not have a clinical course that is distinctly different from classical essential thrombocythemia [48], and should not be considered CML. The significance of *BCR::ABL1* transcripts in this setting requires further investigation. (See "Molecular genetics of chronic myeloid leukemia" and "Clinical manifestations, pathogenesis, and diagnosis of essential thrombocythemia" and "Clinical manifestations and diagnosis of polycythemia vera".)

Although the clinical course and initial blood findings of patients with the other myeloproliferative neoplasms can sometimes overlap with those of CML, the bone marrow evaluation can be helpful in distinguishing them apart. CML has small "dwarf" megakaryocytes, and the other myeloproliferative neoplasms typically have large atypical megakaryocytes. Evaluation for the Ph chromosome by cytogenetics, *BCR::ABL1* by FISH, or high levels of *BCR::ABL1* transcripts by RT-PCR will usually resolve any difficult cases.

Rare cases have been reported in which patients with *JAK2* V617F mutations (commonly seen in the non-CML myeloproliferative neoplasms) later develop the Ph chromosome and *BCR::ABL1*

[49]. These are quite unusual and are likely cases of non-CML myeloproliferative neoplasms which develop superimposed CML. The opposite sequence of events has also been reported.

Other Philadelphia chromosome-positive malignancies — The Ph chromosome is found in 20 to 30 percent of adults with acute precursor B cell lymphoblastic leukemia (ALL), 5 to 10 percent of childhood ALL, and about 1 percent of adult AML [50]. Patients with Ph-positive acute leukemia are heterogeneous when analyzed at the molecular level. At least some of these patients probably represent CML presenting in blast crisis phase, but others may represent de novo acute leukemia. Ph-positive AML, like Ph-positive ALL and CML lymphoid blast crisis, is characterized by frequent chromosomal deletions of the immunoglobulin heavy chain (*IgH*) region that are not found in CML myeloid blast crisis, supporting a distinct origin of this disease [51].

Often one can identify the blastic disease and recognize CML in the background in patients who have CML that is presenting in blasts crisis. For example, a patient might present with a white blood cell count of 600,000/microL and have 60 percent lymphoblasts, but 40 percent of the cells (240,000/microL) are immature with maturing neutrophils, a "myelocyte bulge," and basophilia. This is clearly CML with a lymphoid blast crisis superimposed. In such a case the Ph chromosome will be in the lymphoblasts and in the neutrophils, whereas in Ph+ ALL the clone is restricted to the lymphoid cells [52].

The Ph chromosome has been reported rarely in other hematologic malignancies, including multiple myeloma and B cell non-Hodgkin lymphoma [53,54]. (See "Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma" and "Clinical manifestations, pathologic features, and diagnosis of precursor T cell acute lymphoblastic leukemia/lymphoma" and "Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia" and "Classification, cytogenetics, and molecular genetics of acute lymphoblastic leukemia/lymphoma", section on 't(9;22); BCR::ABL1'.)

PROGNOSIS

Outcomes — The prognosis of patients with CML has improved dramatically since the incorporation of BCR::ABL1 tyrosine kinase inhibitors (TKIs) into the initial treatment such that the life expectancy approaches that of the general population [55,56].

This improvement over time was illustrated in a study of the Surveillance, Epidemiology, and End Results (SEER) database that analyzed the outcomes of 5138 patients diagnosed with CML

before and after the general availability of TKIs [55]. Five-year overall survival (OS) rates in 2000 and 2005, according to patient age at diagnosis, were as follows:

- 15 to 44 years – OS 72 versus 86 percent (HR 0.424; 95% CI 0.275-0.654)
- 45 to 64 years – OS 68 versus 76 percent (HR 0.716; 95% CI 0.528-0.971)
- 65 to 74 years – OS 38 versus 51 percent (HR 0.692; 95% CI 0.518-0.924)
- 75 to 84 years – OS 19 versus 36 percent (HR 0.568; 95% CI 0.441-0.734)

A multicenter longitudinal study of patients treated with imatinib beginning before 2005 who achieved complete cytogenetic remission within two years demonstrated an age-adjusted mortality rate that was not significantly different from that of the general population [57].

Attempts have been made to identify patients at diagnosis who have an unfavorable prognosis [58-65]. By far the strongest single predictor of outcome in patients with CML is the stage of disease at the time of diagnosis. Patients with chronic phase at the time of diagnosis can have years of disease control with treatment while those in accelerated phase or blast crisis have a much poorer prognosis.

This observation also holds for the subgroup of patients harboring the BCR::ABL1 T315I mutation, which is resistant to the majority of the currently available TKIs. In a study of 222 such patients, median OS was 22, 28, 4, and 5 months when this mutation was detected during chronic phase, accelerated phase, blast phase, or Ph+ ALL, respectively [66].

As the risk of dying from CML has decreased, the prognostic impact of comorbidities has taken on greater importance. In one large study, the estimated OS rate at eight years decreased with increasing comorbidity as measured by the Charlson Comorbidity Index (CCI) [67]. OS estimates were 94, 89, 78, and 46 percent for patients with a CCI of 2, 3 to 4, 5 to 6, and ≥ 7 , respectively. These results demonstrate that CML is usually well managed with available therapies and deaths are more often likely to occur due to other medical problems. As patients enrolled on a prospective clinical trial are typically more medically fit than the general CML population (due to eligibility requirements), the clinical outcomes for non-protocol candidates may be even more stark.

Scoring systems — A validated prognostic model for CML should be used to assess prognosis and to aid selection of a TKI for initial therapy of CML. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Choosing a TKI'.)

The Sokal, Euro (Hasford), EUTOS, or ELTS (EUTOS long-term survival score) are all acceptable for assessing prognosis in CML (table 5) [58,63,68,69]. The Sokal, Hasford, and ELTS scoring

systems stratify patients into three risk groups: low, intermediate, and high; EUTOS stratifies patients into low and high risk groups.

ELTS provides the best discrimination for the probability of CML-specific death and, unlike the other prognostic models, was derived from survival data that reflect treatment of CML with TKIs [69,70]. (See 'ELTS' below.)

The Sokal and Hasford scores have similar levels of performance, but were derived from data sets that included some patients who were treated before the routine use of TKIs [59].

Sokal — The Sokal prognostic score is based on four clinical features: spleen size, percent blasts, age, and platelet count $>700,000/\text{microL}$ ($700 \times 10^9/\text{L}$) (calculator 1) [58].

Hasford (Euro) — The Hasford (Euro) score adds eosinophilia and basophilia to the clinical features of the Sokal score (described above) (Euro score calculator) [63].

EUTOS — The EUTOS (EUTOS score calculator) is based on age, spleen size, peripheral blood blast count, and platelet count.

ELTS — The ELTS score is based on age, spleen size, peripheral blood blast count, and platelet count (calculator 2) (ELTS score calculator).

Use of prognostic scores for management of CML is described separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'CML risk score'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic myeloid leukemia".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient education" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Chronic myeloid leukemia (CML) (The Basics)")
 - Beyond the Basics topics (see "Patient education: Chronic myeloid leukemia (CML) in adults (Beyond the Basics)")
-

SUMMARY

- **Definition** – Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) associated with the t(9;22)(q34;q11) chromosomal rearrangement, the so-called Philadelphia chromosome (Ph). The rearrangement creates the BCR::ABL1 fusion protein, which drives excessive accumulation of immature and maturing granulocytic cells in blood, bone marrow, liver, and spleen.
- **Clinical manifestations** – CML can be considered a biphasic or triphasic disease. Most patients present with chronic phase (CP) CML, which is relatively indolent, but occasional patients present with accelerated phase (AP) or blast crisis (BC), which are more advanced disease phases. (See 'Clinical manifestations' above.)

Many patients with CP CML are asymptomatic and the disease is first detected with a routine blood test; other patients may describe constitutional symptoms (fever, sweats, weight loss), abdominal discomfort, or early satiety due to an enlarged spleen. Patients who present with AP or BC CML may have infections, anemia, bleeding, prominent constitutional symptoms, or increasing splenomegaly.

- **Pathologic features**

- **Complete blood count (CBC)/differential count** – In CP CML, there is marked leukocytosis (median 80,000/microL), a left shift with circulating immature myeloid cells, blasts are typically <2 percent, and eosinophils and/or basophils are often increased. CBC may also reveal anemia, polycythemia, thrombocytosis, or thrombocytopenia. Blood counts are generally more extreme in AP and BC CML.

- **Blood smear** – Myeloid cells in CP CML range from myeloblasts to mature neutrophils (picture 1), but they generally are not strikingly dysplastic. AP and BC exhibit more extreme left shift and blasts are markedly increased.
- **Bone marrow** – Marrow in CP is generally hypercellular with an increase of granulocytic cells (picture 2) and blasts are usually <5 percent of myeloid cells. Other findings include an increased myeloid:erythroid ratio; megakaryocytes may be normal, diminished, or increased; and there may be reticulin fibrosis. AP and BC exhibit more blasts; for most patients these are myeloid blasts, but up to one-quarter have lymphoid blasts.
- **Diagnosis** – The diagnosis of CML requires detection of the t(9;22)(q34;q11) chromosomal rearrangement (the Ph chromosome) by karyotypic banding (figure 1) or fluorescence in situ hybridization (FISH) and/or *BCR::ABL1* RNA transcripts by reverse transcription polymerase chain reaction (RT-PCR). (See 'Diagnosis' above.)
- **Differential diagnosis** – Disorders that may resemble CML include (see 'Differential diagnosis' above):
 - **Leukemoid reaction** – Marked accumulation of non-malignant granulocytic cells in response to an infection or other inflammatory stimulus
 - **Other MPNs** – Polycythemia vera, essential thrombocythemia, chronic myelomonocytic leukemia
 - **Other leukemias** – Acute myeloid leukemia, Ph+ acute lymphoblastic leukemia/lymphoblastic lymphoma
- **Prognosis** – Prognosis should be assessed using either the Sokal, Euro (Hasford), EUTOS, or ELTS (EUTOS long-term survival score) models (table 5). (See 'Scoring systems' above.)

Use of UpToDate is subject to the Terms of Use.

REFERENCES

1. Van Etten RA. c-Abl regulation: a tail of two lipids. *Curr Biol* 2003; 13:R608.
2. Konopka JB, Witte ON. Detection of c-abl tyrosine kinase activity in vitro permits direct comparison of normal and altered abl gene products. *Mol Cell Biol* 1985; 5:3116.
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67:7.

4. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* 2010; 116:3724.
5. Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer* 2011; 105:1684.
6. Chen Y, Wang H, Kantarjian H, Cortes J. Trends in chronic myeloid leukemia incidence and survival in the United States from 1975 to 2009. *Leuk Lymphoma* 2013; 54:1411.
7. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. *N Engl J Med* 1999; 341:164.
8. Moloney WC. Radiogenic leukemia revisited. *Blood* 1987; 70:905.
9. Björkholm M, Kristinsson SY, Landgren O, Goldin LR. No familial aggregation in chronic myeloid leukemia. *Blood* 2013; 122:460.
10. Bellanné-Chantelot C, Chaumarel I, Labopin M, et al. Genetic and clinical implications of the Val617Phe JAK2 mutation in 72 families with myeloproliferative disorders. *Blood* 2006; 108:346.
11. Kim DH, Lee ST, Won HH, et al. A genome-wide association study identifies novel loci associated with susceptibility to chronic myeloid leukemia. *Blood* 2011; 117:6906.
12. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Cancer* 2012; 118:3123.
13. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *Br J Haematol* 1997; 96:111.
14. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC Press, Lyon 2008.
15. Spiers AS, Bain BJ, Turner JE. The peripheral blood in chronic granulocytic leukaemia. Study of 50 untreated Philadelphia-positive cases. *Scand J Haematol* 1977; 18:25.
16. Melo JV, Myint H, Galton DA, Goldman JM. P190BCR-ABL chronic myeloid leukaemia: the missing link with chronic myelomonocytic leukaemia? *Leukemia* 1994; 8:208.
17. Ravandi F, Cortes J, Albitar M, et al. Chronic myelogenous leukaemia with p185(BCR/ABL) expression: characteristics and clinical significance. *Br J Haematol* 1999; 107:581.
18. Cortes JE, Talpaz M, Giles F, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. *Blood* 2003; 101:3794.

19. Fabarius A, Leitner A, Hochhaus A, et al. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML Study IV. *Blood* 2011; 118:6760.
20. Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. *Blood* 2016; 127:2742.
21. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127:2391.
22. Niemeyer CM, Kratz C. Juvenile myelomonocytic leukemia. *Curr Oncol Rep* 2003; 5:510.
23. Koike K, Matsuda K. Recent advances in the pathogenesis and management of juvenile myelomonocytic leukaemia. *Br J Haematol* 2008; 141:567.
24. Emanuel PD. Juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. *Leukemia* 2008; 22:1335.
25. Aricò M, Biondi A, Pui CH. Juvenile myelomonocytic leukemia. *Blood* 1997; 90:479.
26. Passmore SJ, Chessells JM, Kempski H, et al. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia in the UK: a population-based study of incidence and survival. *Br J Haematol* 2003; 121:758.
27. Loh ML, Sakai DS, Flotho C, et al. Mutations in CBL occur frequently in juvenile myelomonocytic leukemia. *Blood* 2009; 114:1859.
28. De Filippi P, Zecca M, Lisini D, et al. Germ-line mutation of the NRAS gene may be responsible for the development of juvenile myelomonocytic leukaemia. *Br J Haematol* 2009; 147:706.
29. Niemeyer CM, Kang MW, Shin DH, et al. Germline CBL mutations cause developmental abnormalities and predispose to juvenile myelomonocytic leukemia. *Nat Genet* 2010; 42:794.
30. Kato M, Yasui N, Seki M, et al. Aggressive transformation of juvenile myelomonocytic leukemia associated with duplication of oncogenic KRAS due to acquired uniparental disomy. *J Pediatr* 2013; 162:1285.
31. Vardiman JW, Pierre R, Bain B, et al. Chronic myelomonocytic leukemia. In: *World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds), IARC Press, Lyon 2001. p.49.
32. Hernández JM, del Cañizo MC, Cuneo A, et al. Clinical, hematological and cytogenetic characteristics of atypical chronic myeloid leukemia. *Ann Oncol* 2000; 11:441.

33. Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. *Blood* 2013; 122:1707.
34. McClure RF, Dewald GW, Hoyer JD, Hanson CA. Isolated isochromosome 17q: a distinct type of mixed myeloproliferative disorder/myelodysplastic syndrome with an aggressive clinical course. *Br J Haematol* 1999; 106:445.
35. Piazza R, Valletta S, Winkelmann N, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. *Nat Genet* 2013; 45:18.
36. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med* 2013; 368:1781.
37. Wang SA, Hasserjian RP, Fox PS, et al. Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. *Blood* 2014; 123:2645.
38. Bain BJ. Eosinophilic leukaemias and the idiopathic hypereosinophilic syndrome. *Br J Haematol* 1996; 95:2.
39. Oliver JW, Deol I, Morgan DL, Tonk VS. Chronic eosinophilic leukemia and hypereosinophilic syndromes. Proposal for classification, literature review, and report of a case with a unique chromosomal abnormality. *Cancer Genet Cytogenet* 1998; 107:111.
40. Bain BJ. Cytogenetic and molecular genetic aspects of eosinophilic leukaemias. *Br J Haematol* 2003; 122:173.
41. Kurzrock R, Bueso-Ramos CE, Kantarjian H, et al. BCR rearrangement-negative chronic myelogenous leukemia revisited. *J Clin Oncol* 2001; 19:2915.
42. Reilly JT. Chronic neutrophilic leukaemia: a distinct clinical entity? *Br J Haematol* 2002; 116:10.
43. Elliott MA. Chronic neutrophilic leukemia: a contemporary review. *Curr Hematol Rep* 2004; 3:210.
44. Böhm J, Schaefer HE. Chronic neutrophilic leukaemia: 14 new cases of an uncommon myeloproliferative disease. *J Clin Pathol* 2002; 55:862.
45. Beekman R, Valkhof M, van Strien P, et al. Prevalence of a new auto-activating colony stimulating factor 3 receptor mutation (CSF3R-T595I) in acute myeloid leukemia and severe congenital neutropenia. *Haematologica* 2013; 98:e62.
46. Pardanani A, Lasho TL, Laborde RR, et al. CSF3R T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. *Leukemia* 2013; 27:1870.
47. Stoll DB, Peterson P, Exten R, et al. Clinical presentation and natural history of patients with essential thrombocythemia and the Philadelphia chromosome. *Am J Hematol* 1988; 27:77.

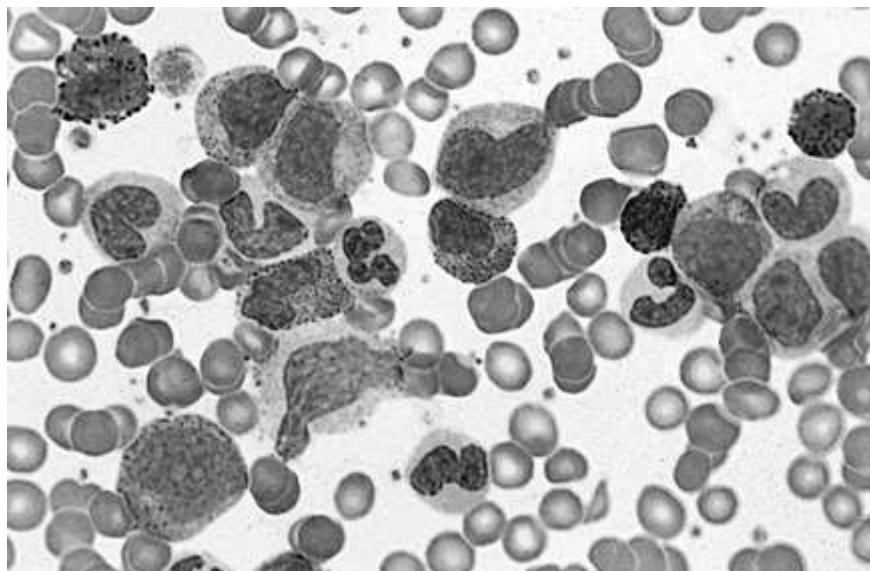
48. Blickstein D, Aviram A, Luboshitz J, et al. BCR-ABL transcripts in bone marrow aspirates of Philadelphia-negative essential thrombocytopenia patients: clinical presentation. *Blood* 1997; 90:2768.
49. Krämer A. JAK2-V617F and BCR-ABL--double jeopardy? *Leuk Res* 2008; 32:1489.
50. Westbrook CA, Hooberman AL, Spino C, et al. Clinical significance of the BCR-ABL fusion gene in adult acute lymphoblastic leukemia: a Cancer and Leukemia Group B Study (8762). *Blood* 1992; 80:2983.
51. Nacheva EP, Grace CD, Brazma D, et al. Does BCR/ABL1 positive acute myeloid leukaemia exist? *Br J Haematol* 2013; 161:541.
52. Anastasi J, Feng J, Dickstein JI, et al. Lineage involvement by BCR/ABL in Ph+ lymphoblastic leukemias: chronic myelogenous leukemia presenting in lymphoid blast vs Ph+ acute lymphoblastic leukemia. *Leukemia* 1996; 10:795.
53. Martiat P, Mecucci C, Nizet Y, et al. P190 BCR/ABL transcript in a case of Philadelphia-positive multiple myeloma. *Leukemia* 1990; 4:751.
54. Mitani K, Sato Y, Tojo A, et al. Philadelphia chromosome positive B-cell type malignant lymphoma expressing an aberrant 190 kDa bcr-abl protein. *Br J Haematol* 1990; 76:221.
55. Brunner AM, Campigotto F, Sadrzadeh H, et al. Trends in all-cause mortality among patients with chronic myeloid leukemia: a Surveillance, Epidemiology, and End Results database analysis. *Cancer* 2013; 119:2620.
56. Bower H, Björkholm M, Dickman PW, et al. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. *J Clin Oncol* 2016; 34:2851.
57. Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. *J Natl Cancer Inst* 2011; 103:553.
58. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood* 1984; 63:789.
59. Bonifazi F, De Vivo A, Rosti G, et al. Testing Sokal's and the new prognostic score for chronic myeloid leukaemia treated with alpha-interferon. Italian Cooperative Study Group on Chronic Myeloid Leukaemia. *Br J Haematol* 2000; 111:587.
60. Kvasnicka HM, Thiele J, Schmitt-Graeff A, et al. Prognostic impact of bone marrow erythropoietic precursor cells and myelofibrosis at diagnosis of Ph1+ chronic myelogenous leukaemia--a multicentre study on 495 patients. *Br J Haematol* 2001; 112:727.

61. Kvasnicka HM, Thiele J, Schmitt-Graeff A, et al. Bone marrow features improve prognostic efficiency in multivariate risk classification of chronic-phase Ph(1+) chronic myelogenous leukemia: a multicenter trial. *J Clin Oncol* 2001; 19:2994.
62. Sokal risk score calculator available online at: www.roc.se/sokal.asp (Accessed on February 19, 2009).
63. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst* 1998; 90:850.
64. Sinclair PB, Nacheva EP, Leversha M, et al. Large deletions at the t(9;22) breakpoint are common and may identify a poor-prognosis subgroup of patients with chronic myeloid leukemia. *Blood* 2000; 95:738.
65. Luatti S, Castagnetti F, Marzocchi G, et al. Additional chromosomal abnormalities in Philadelphia-positive clone: adverse prognostic influence on frontline imatinib therapy: a GIMEMA Working Party on CML analysis. *Blood* 2012; 120:761.
66. Nicolini FE, Mauro MJ, Martinelli G, et al. Epidemiologic study on survival of chronic myeloid leukemia and Ph(+) acute lymphoblastic leukemia patients with BCR-ABL T315I mutation. *Blood* 2009; 114:5271.
67. Saussele S, Krauss MP, Hehlmann R, et al. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. *Blood* 2015; 126:42.
68. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. *Blood* 2011; 118:686.
69. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia* 2016; 30:48.
70. Pfirrmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. *Leukemia* 2020; 34:2138.

Topic 4543 Version 52.0

GRAPHICS

Chronic myeloid leukemia blood smear

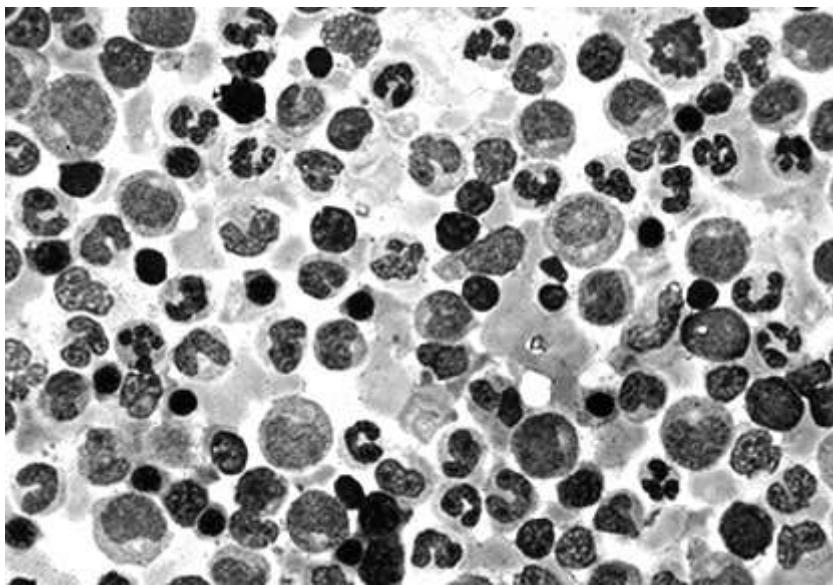


Characteristic peripheral blood smear of chronic myeloid leukemia shows basophilia and granulocytosis with neutrophils and immature granulocytes.

Reproduced with permission from: McClatchey, KD, MD, DDS. Clinical Laboratory Medicine, 2nd Edition. Philadelphia: Lippincott Williams & Wilkins, 2002. Copyright ©2002 Lippincott Williams & Wilkins.

Graphic 56954 Version 3.0

Bone marrow aspirate in chronic myelogenous leukemia

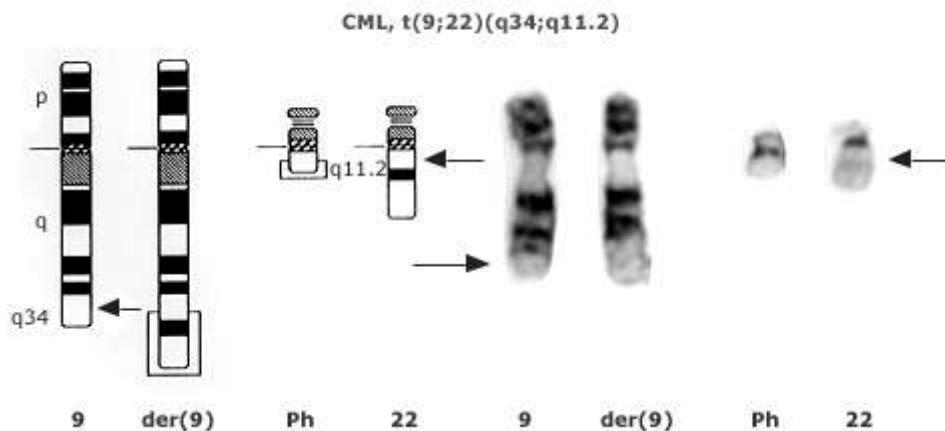


Bone marrow aspirate from a patient with chronic myelogenous leukemia shows hyperplasia of elements of the granulocytic series (eg, promyelocytes, myelocytes, metamyelocytes, band forms, and mature granulocytes).

Courtesy of David S Rosenthal, MD and Anna J Mitus, MD.

Graphic 68724 Version 2.0

The Philadelphia chromosome in chronic myeloid leukemia

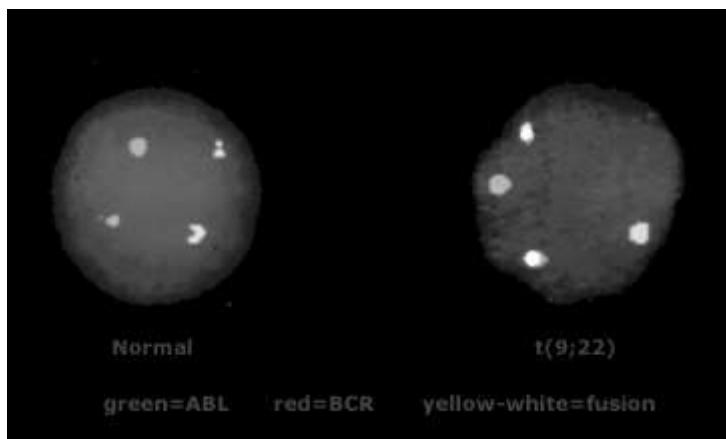


G-band ideograms (left) and partial karyotype (right) of the CML-associated chromosome translocation t(9;22)(q34;q11.2). Breakpoints are indicated with arrows on the normal chromosome homologs. Translocated segments are framed on the der(9) and Ph ideograms. The translocation results in a slightly longer chromosome 9 [der(9)] and a shorter chromosome 22 [der(22)], which is termed the Philadelphia (Ph) chromosome.

Courtesy of Athena Cherry, PhD.

Graphic 62227 Version 2.0

Interphase fluorescence in situ hybridization (FISH) images of normal and t(9;22) positive nuclei



The dual-color ABL (green) and BCR (red) probes span their respective breakpoint regions, producing two red and two green signals in a normal nucleus (on the left). In the t(9;22) cell (on the right), the single red and green signals correspond to the normal ABL and BCR genes, respectively, while the two yellow-white fusion signals correspond to the Ph chromosome and the reciprocal balanced translocation product (derivative chromosome 9).

Photo courtesy of Athena Cherry, PhD.

Graphic 73543 Version 1.0

WHO diagnostic criteria for juvenile myelomonocytic leukemia

I. Clinical and hematologic features (all 4 features mandatory)

- Peripheral blood monocyte count $\geq 1 \times 10^9/L$
- Blast percentage in peripheral blood and bone marrow $< 20\%$
- Splenomegaly
- Absence of Philadelphia chromosome (*BCR/ABL1* rearrangement)

II. Genetic studies (1 finding sufficient)

- Somatic mutation in *PTPN11** or *KRAS** or *NRAS**
- Clinical diagnosis of NF1 or *NF1* mutation
- Germ line *CBL* mutation and loss of heterozygosity of *CBL* ¶

III. For patients without genetic features, besides the clinical and hematologic features listed under I, the following criteria must be fulfilled:

- Monosomy 7 or any other chromosomal abnormality or at least 2 of the following criteria:
 - Hemoglobin F increased for age
 - Myeloid or erythroid precursors on peripheral blood smear
 - GM-CSF hypersensitivity in colony assay
 - Hyperphosphorylation of STAT5

WHO: World Health Organization; NF1: neurofibromatosis type 1; GM-CSF: granulocyte-macrophage colony-stimulating factor; JMML: juvenile myelomonocytic leukemia.

* Germ line mutations (indicating Noonan syndrome) need to be excluded.

¶ Occasional cases with heterozygous splice site mutations.

Republished with permission of the American Society of Hematology, from Locatelli F, Niemeyer CM. How I treat juvenile myelomonocytic leukemia. Blood 2015; 125:1083. Copyright © 2015; permission conveyed through Copyright Clearance Center, Inc.

Modified in:

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127:2391.

WHO diagnostic criteria atypical chronic myeloid leukemia, BCR-ABL1 negative

- Peripheral blood leukocytosis due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes, metamyelocytes) comprising $\geq 10\%$ of leukocytes
- Dysgranulopoiesis, which may include abnormal chromatin clumping
- No or minimal absolute basophilia; basophils usually $< 2\%$ of leukocytes
- No or minimal absolute moncytosis; monocytes $< 10\%$ of leukocytes
- Hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
- $< 20\%$ blasts in the blood and bone marrow
- No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement, or *PCM1-JAK2*
- Not meeting WHO criteria for *BCR-ABL1⁺* CML, PMF, PV, or ET*

Diagnosis of atypical CML, BCR-ABL1- requires meeting all of the criteria above.

aCML: atypical chronic myeloid leukemia; CML: chronic myeloid leukemia; CNL: chronic neutrophilic leukemia; ET: essential thrombocythemia; MPN: myeloproliferative neoplasm; PMF: primary myelofibrosis; PV: polycythemia vera; WHO: World Health Organization

* Cases of MPN, particularly those in accelerated phase and/or in post-polycythemic or post-essential thrombocythemic myelofibrosis, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the bone marrow and/or MPN-associated mutations (in *JAK2*, *CALR*, or *MPL*) tend to exclude a diagnosis of aCML. Conversely, a diagnosis of aCML is supported by the presence of *SETBP1* and/or *ETNK1* mutations. The presence of a *CSF3R* mutation is uncommon in aCML and if detected should prompt a careful morphologic review to exclude an alternative diagnosis of CNL or other myeloid neoplasm.

Republished with permission of the American Society of Hematology, from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391. Copyright © 2016; permission conveyed through Copyright Clearance Center, Inc.

WHO criteria: chronic eosinophilic leukemia and hypereosinophilic syndrome

Required
Persistent peripheral blood eosinophilia ($\geq 1500/\text{microL}$)
Increased numbers of bone marrow eosinophils
Myeloblasts <20 percent in peripheral blood or bone marrow
Conditions to be excluded
Reactive eosinophilia
Allergy
Parasitic diseases
Infectious diseases
Pulmonary disease (eg, hypersensitivity pneumonia, Loeffler's pneumonia)
Collagen vascular disorders
Neoplastic disorders with secondary reactive eosinophilia
T cell lymphomas (eg, mycosis fungoides, Sézary syndrome)
Hodgkin lymphoma
Acute lymphoblastic leukemia
Mastocytosis
Neoplastic disorders in which eosinophils are part of the neoplastic clone
Chronic myeloid leukemia (Ph1 + or BCR/ABL positive)
Acute myeloid leukemia [eg, FAB M4Eo with inv(16), t(16;16)(p13;q22)]
Other myeloproliferative disorders (eg, polycythemia vera, essential thrombocythosis, chronic idiopathic myelofibrosis)
T cell population with aberrant phenotype and abnormal cytokine production
Diagnosis
Hypereosinophilic syndrome:
This diagnosis is made if there is no demonstrable disease that could cause the eosinophilia, no abnormal T cell population, and no evidence for a clonal myeloid malignancy.
Chronic eosinophilic leukemia:
This diagnosis is made if all of the above exclusions have been met and if the myeloid cells demonstrate a clonal chromosomal abnormality, or are shown to be clonal by other means, or

blast cells are present in the peripheral blood (> 2 percent) or are increased in the bone marrow (>5 to <19 percent of nucleated cells).

Adapted from: Bain B, et al. *Chronic eosinophilic leukaemia and the hypereosinophilic syndrome*. In: Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds). *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, IARC Press, Lyon 2001. p.49. Permission granted from Harris NL and Vardiman JW.

Graphic 54770 Version 3.0

WHO diagnostic criteria for chronic neutrophilic leukemia

1. Peripheral blood WBC $\geq 25 \times 10^9 / L$
Segmented neutrophils plus band forms $\geq 80\%$ of WBCs
Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) $< 10\%$ of WBC
Myeloblasts rarely observed
Monocyte count $< 1 \times 10^9 / L$
No dysgranulopoiesis
2. Hypercellular bone marrow
Neutrophil granulocytes increased in percentage and number
Neutrophil maturation appears normal
Myeloblasts $< 5\%$ of nucleated cells
3. Not meeting WHO criteria for <i>BCR-ABL1</i> ⁺ CML, PV, ET, or PMF
4. No rearrangement of <i>PDGFRA</i> , <i>PDGFRB</i> , or <i>FGFR1</i> , or <i>PCM1-JAK2</i>
5. Presence of <i>CSF3R</i> T618I or other activating <i>CSF3R</i> mutation
or
In the absence of a <i>CSF3R</i> mutation, persistent neutrophilia (at least 3 months), splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies

The diagnosis of chronic neutrophilic leukemia requires all five criteria.

CML: chronic myeloid leukemia; ET: essential thrombocythemia; PV: polycythemia vera; PMF: primary myelofibrosis; WBC: white blood cell count; WHO: World Health Organization

Republished with permission of the American Society of Hematology, from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391. Copyright © 2016; permission conveyed through Copyright Clearance Center, Inc.

Prognostic scoring systems for newly diagnosed chronic myeloid leukemia*

Scoring system	Calculator Link	Risk groups
EUTOS score ^[1]	www.leukemia-net.org/content/leukemias/cml/eutos_score/	Low risk, high risk
Euro (Hasford) score ^[2]	www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/	Low risk, intermediate risk, high risk
Sokal score ^[3]	www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/	Low risk, intermediate risk, high risk
The EUTOS long-term survival score (ELTS) ^[4]	www.leukemia-net.org/content/leukemias/cml/elts_score/	Low risk, intermediate risk, high risk

* These scoring systems were designed for patients with newly diagnosed chronic myeloid leukemia (CML) who have not yet received any treatment, including hydroxyurea. In addition, the EUTOS score was specifically designed to predict outcomes among patients undergoing initial treatment with imatinib.

References:

1. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. *Blood* 2011; 118:686.
2. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst* 1998; 90:850.
3. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood* 1984; 63:789.
4. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia* 2016; 30:48.

→