

# Accelerated phase chronic myeloid leukemia: Diagnosis and treatment

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## INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with t(9;22) (q34;q11), the so-called Philadelphia chromosome. This chromosomal rearrangement creates the *BCR-ABL1* fusion gene, which encodes BCR-ABL1, a constitutively active tyrosine kinase. Up to 90 percent of patients with CML present with chronic phase (CP) CML, which is a relatively indolent disorder that responds well to treatment with a BCR-ABL1 tyrosine kinase inhibitor (TKI). The remainder of patients present with advanced CML: either accelerated phase (AP) CML or blast phase (BP; also called blast crisis) CML.

AP CML is distinguished from CP CML and BP CML according to myeloblast count, percentage of basophils, additional chromosomal abnormalities, and other clinico-pathologic features. Some patients initially present with AP CML (de novo AP CML), while others have disease that initially presented as CP CML, but transformed (ie, progressed) to AP while receiving treatment with a TKI. The distinction between de novo AP CML and transformed AP CML affects treatment decisions and prognosis.

This topic discusses the diagnosis and management of AP CML.

Treatment of CP CML, blast crisis CML, and use of hematopoietic cell transplantation (HCT) for CML are discussed separately.

- (See "Overview of the treatment of chronic myeloid leukemia".)
  - (See "Initial treatment of chronic myeloid leukemia in chronic phase".)
  - (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)
  - (See "Treatment of chronic myeloid leukemia in blast crisis".)
  - (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)
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## PRETREATMENT EVALUATION

Pretreatment evaluation of a patient with CML should include history and physical examination, performance status (table 1), and laboratory and clinical studies that enable accelerated phase (AP) CML to be distinguished from chronic phase (CP) CML and blast phase (BP) CML and establish baseline molecular studies for monitoring response to treatment.

Patients with transformed AP CML (ie, AP CML that arose while undergoing treatment for CP CML) must also have molecular analysis for *BCR-ABL1* mutations. (See 'Mutation testing' below.)

Initial evaluation, diagnosis, and differential diagnosis of CML are discussed separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Pretreatment evaluation'.)

### Clinical and laboratory

- **History** should document:
  - B symptoms (ie, unexplained fevers, drenching sweats, weight loss), anorexia, abdominal pain/fullness, bone pain
  - Comorbid conditions (eg, cardiac dysrhythmias, heart failure, pancreatitis, liver disease, diabetes mellitus)
  - Adherence to and tolerance for *BCR-ABL1* tyrosine kinase inhibitor (TKI), if used previously
- **Physical examination** should note splenomegaly, hepatomegaly, and stigmata of bleeding/bruising.
- **Performance status** (table 1)

- **Laboratory**

- Complete blood count (CBC) with differential count
- Serum chemistries, including electrolytes, glucose, renal function tests, liver function tests
- Hepatitis B serology

- **Clinical tests**

- Electrocardiogram (EKG)
- Chest radiograph
- **BCR-ABL1** – Quantitative reverse transcription polymerase chain reaction (qPCR) for *BCR-ABL1* in blood or bone marrow, to establish a baseline for subsequent response monitoring.
- **Bone marrow morphology**, including percentage of blasts, promyelocytes, and basophils.

Diagnostic criteria for distinguishing AP CML from CP CML and BP CML are described below. (See 'Diagnosis of AP CML' below.)

- **Karyotype** – Giemsa-stained chromosome banding analysis (CBA) to confirm the presence of t(9;22) (q34;q11)/Philadelphia chromosome (Ph) **and** identify additional chromosomal abnormalities (ACA) in Ph+ cells.

Fluorescence in situ hybridization (FISH) is not an adequate substitute for CBA, because it will not detect ACAs, but FISH should be performed if Ph is not detected by CBA.

**Mutation testing** — *BCR-ABL1* kinase domain mutations inform the choice of TKI, as described below. (See 'Mutation-guided' below.)

Mutation analysis is required for patients with transformed AP CML (ie, AP CML that arose during TKI treatment for CP CML), but it is not required for patients who initially presented with AP CML (ie, de novo AP CML).

**Hematopoietic cell transplantation evaluation** — For patients who may require allogeneic hematopoietic cell transplantation (HCT), it is important to determine eligibility and initiate a donor search. (See "Determining eligibility for allogeneic hematopoietic cell transplantation".)

The timing for this evaluation is influenced by whether the patient has de novo AP CML versus transformed AP CML. All patients with transformed AP CML, except those who are frail, should be referred promptly; for patients with de novo AP CML, many experts await the response to initial therapy before referring the patient for evaluation. (See 'de novo versus transformed AP' below.)

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## DIAGNOSIS OF AP CML

The initial evaluation, diagnosis, and differential diagnosis of CML are discussed separately. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia".)

We favor use of the World Health Organization (WHO) criteria to diagnose AP CML (table 2). The WHO model defines AP CML as 10 to 19 percent blasts in blood or bone marrow, which distinguishes AP CML from chronic phase (CP) CML (<10 percent blasts) and blast phase (BP; ≥20 percent blasts). These criteria are consistent with contemporary criteria for the diagnosis of acute myeloid leukemia (AML) and it reflects the important prognostic role of the blast count in CML [1,2]. By contrast, the European LeukemiaNet (ELN) [3] and MD Anderson Cancer Center (MDACC) [4] models use 30 percent blasts and/or promyelocytes to distinguish AP CML from CP CML; other differences between diagnostic models are presented below. It should be noted that, historically, most clinical studies used a threshold of 30 percent blasts to define BP CML.

In addition to establishing the diagnosis of AP CML, it is important to distinguish between de novo AP CML and transformed AP CML, as described below. (See 'de novo versus transformed AP' below.)

**World Health Organization** — World Health Organization (WHO) criteria diagnose AP CML based on the presence of any of the following [2]:

- **Blasts** – 10 to 19 percent blasts in blood or bone marrow.
- **Basophils** – ≥20 percent basophils in blood.
- **Thrombocytopenia** – Platelets persistently <100,000/microL (<100 × 10<sup>9</sup>/L) unrelated to therapy.
- **Additional chromosomal abnormalities (ACA)** – Major route ACAs in Philadelphia chromosome-positive (Ph+) cells detected at diagnosis (eg, second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2. Other chromosomal findings in Ph+ cells are considered minor route ACAs.

- **New ACA while on treatment** – Development of any new ACA (ie, major or minor route) in Ph+ cells while receiving treatment with a BCR-ABL1 tyrosine kinase inhibitor (TKI).

According to WHO criteria, BP CML is diagnosed and distinguished from AP CML based on either infiltrative blasts in an extramedullary site or ≥20 percent blasts in blood or bone marrow [2].

## Other models

- **European LeukemiaNet (ELN)** – ELN diagnostic criteria for AP CML [3] follow:
  - Blasts in blood or marrow 15 to 29 percent or blasts plus promyelocytes >30 percent (with <30 percent blasts)
  - Basophils ≥20 percent in blood
  - Persistent thrombocytopenia  $<100 \times 10^9/L$ , unrelated to therapy
  - Major route ACA (described above) in Ph+ cells that develops while receiving TKI treatment

In the ELN model, major route ACAs establish the diagnosis of AP CML only if they develop while on TKI treatment; by contrast, the WHO diagnoses AP CML if a major route ACA is present at the time of initial diagnosis or if any ACA develops while on treatment [2,3].

- **MDACC (MD Anderson Cancer Center)** – The MDACC model diagnoses AP CML as follows [4]:
  - Blasts in blood or marrow 15 to 29 percent; blasts plus promyelocytes >30 percent
  - Basophils ≥20 percent in blood
  - Persistent thrombocytopenia  $<100 \times 10^9/L$ , unrelated to therapy
  - ACA (either major route ACA or other) in Ph+ cells
- **Sokal** – We consider the Sokal model to be less helpful, because it is primarily based on clinical findings (eg, progressive splenomegaly, anemia unrelated to therapy, marrow fibrosis, unexplained fever) [5].

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## MANAGEMENT

Our approach to management of CML is consistent with recommendations of the European LeukemiaNet [6] and the US National Comprehensive Cancer Network [7].

**de novo versus transformed AP** — We distinguish between accelerated phase (AP) CML that presents **de novo** versus AP CML that has **transformed** from prior chronic phase (CP) CML, because this influences management and prognosis.

- **de novo CML AP** refers to a patient who presents with AP CML. Patients with de novo AP CML have not previously been treated with a tyrosine kinase inhibitor (TKI; ie, treatment-naïve), because this is the first presentation of the disease.

Management of de novo AP CML is described below. (See 'Treatment of de novo AP CML' below.)

- **Transformed CML AP** refers to a patient whose AP CML arose while being treated with a TKI for CP CML; disease progression may be due to TKI-resistance from a *BCR-ABL1* mutation. Transformed AP CML generally has a less favorable prognosis than de novo AP CML.

For patients with transformed AP CML, it is important to consider adherence with the prior TKI regimen, as poor adherence is a possible cause of disease progression. It is important to ask about adherence to the TKI dose and schedule and use of other medications or herbal supplements that may impair the metabolism of the TKI.

Management of transformed AP CML is described below. (See 'Treatment of transformed AP CML' below.)

**Treatment of de novo AP CML** — For patients who present with **de novo AP CML**, we suggest initial treatment with a second-generation (2G) TKI, rather than allogeneic hematopoietic cell transplantation (HCT) or treatment with imatinib or ponatinib. Compared with the favorable balance of benefits and toxicity of a 2G TKI, for patients with de novo AP CML, the adverse effects and possible treatment-related mortality (TRM) of allogeneic HCT outweigh the potential for disease control and cure. Compared with ponatinib, 2G TKIs have comparable efficacy (except for patients with *BCR-ABL1* T315I mutation), but less toxicity; compared with imatinib, 2G TKIs achieve faster and deeper responses, yet have comparable toxicity (algorithm 1) [8-11].

- **Selection of a TKI** – The choice of a 2G TKI is based on the patient's comorbid conditions and characteristic adverse effects (AEs) (table 3). AEs of 2G TKIs are generally modest, but vary with the individual agent. (See '2G tyrosine kinase inhibitors' below.)

We do not routinely perform mutation testing for patients with de novo AP CML, but some experts favor mutation testing in this setting. If a *BCR-ABL1* T315I mutation was detected, we treat with ponatinib (the only TKI that is effective for this mutation) (see 'Ponatinib' below). Alternative management for a patient with T315I and significant cardiovascular conditions are discussed below. (See 'Other treatments' below.)

- **Outcomes** – There are no prospective data comparing indefinite continuation of a TKI versus allogeneic HCT in patients who achieved a complete cytogenetic response (CCyR) with initial TKI treatment. A single center study reported that treatment with dasatinib or nilotinib was associated with 90 percent CCyR among 21 patients with de novo AP CML [12]. In studies that included both de novo and transformed AP CML, treatment with a 2G TKI was associated with two- to four-year overall survival (OS) in approximately two-thirds of patients [13-15]; however, outcomes with de novo AP CML are probably more favorable than outcomes of the mixed populations of patients (ie, de novo and transformed AP CML) in these studies.

We continue TKI treatment indefinitely. We currently suggest **not** pursuing TKI discontinuation for patients with AP CML who have a robust and prolonged molecular response, as there are no currently-available data to support this approach.

**Treatment of transformed AP CML** — Treatment for **transformed AP CML** is guided by the patient's suitability for allogeneic HCT (algorithm 2), which depends on age, medical fitness, and an appropriate donor, as discussed separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia", section on 'Eligibility'.)

**Transplant-eligible** — For transplant-eligible patients with transformed AP CML, we generally suggest allogeneic HCT rather than treatment with a TKI alone, although treatment choices must be individualized. For transformed AP CML, long-term disease control and possible cure with allogeneic HCT generally outweigh the adverse effects and risk of TRM; by contrast, 2G TKIs or ponatinib have less potential for long-term disease control. Nevertheless, transplantation has not been shown to yield superior survival and some patients who have an excellent response to a TKI may choose to continue the TKI alone, because they place greater weight on avoidance of transplant-related toxicity than on potential benefits of allogeneic HCT.

- **Prior to transplantation** – During the search for a transplant donor, the patient with transformed AP CML should be treated according to the presence of a *BCR-ABL1* kinase domain mutation, comorbid conditions, and characteristic AEs (table 3). Mutation testing is particularly important for transformed AP CML because disease progression usually reflects resistance to the prior TKI. (See 'Tyrosine kinase inhibitor selection' below.)

We generally proceed to allogeneic HCT as soon as the disease can be brought under control with a TKI. Treatment with a TKI does not compromise transplant outcomes or increase transplant-related toxicity [16-22].

- **Outcomes** – Outcomes with allogeneic HCT for AP CML vary because of different eligibility criteria and small numbers of patients in most studies. A retrospective analysis of registry data that included 168 patients with AP CML reported no difference in OS between allogeneic HCT and treatment with a TKI alone; however, the conclusions were limited by varying definitions of AP, inclusion of both de novo and transformed AP CML, and unbalanced numbers of patients in the cohorts [23].

A multicenter study of transplantation in 28 patients with advanced phase CML (ie, both AP CML and BP CML) reported 59 percent three-year OS [24]. A single-center study reported 45 percent long-term survival after allogeneic HCT for 40 patients with advanced phase CML [25]. A registry study reported 37 percent five-year OS among 14 patients with advanced phase CML; non-relapse mortality was 12 percent, but this included patients with AP CML and CP CML [26].

Donor selection, graft source, conditioning regimen, prophylaxis for graft-versus-host disease (GVHD), and further details of outcomes with allogeneic HCT for CML are discussed separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)

**Not transplant-eligible** — For patients with transformed AP CML who are **not** suitable for allogeneic HCT (eg, not medically-fit, no suitable donor, or the patient declines), we select a TKI according to *BCR-ABL1* mutation analysis, comorbid conditions, and toxicity profile, as described below. (See 'Tyrosine kinase inhibitor selection' below.)

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## TYROSINE KINASE INHIBITOR SELECTION

The following should be considered when selecting a *BCR-ABL1* tyrosine kinase inhibitor (TKI) for treatment of accelerated phase (AP) CML:

- **Mutation status** – *BCR-ABL1* kinase domain mutation testing should be performed for all patients with transformed AP CML. We do not routinely perform mutation testing in patients who present with de novo AP CML. Selection of a TKI based on mutation status is discussed below. (See 'Mutation-guided' below.)

- **TKI adverse effects (AEs)** – Each TKI is associated with characteristic AEs (table 3). Selection of a TKI based on AEs is discussed below. (See 'Toxicity-guided' below.)
- **Comorbid conditions** – A history of heart disease, lung conditions, diabetes, pancreatitis, and other comorbid illnesses should be considered in choosing a TKI. (See 'Toxicity-guided' below.)

**Mutation-guided** — Detection of certain *BCR-ABL1* kinase domain mutations contraindicates particular TKIs:

- **Bosutinib** – Avoid bosutinib for T315I, V299L, G250E, or F317L mutation.
- **Dasatinib** – Avoid dasatinib for T315I/A, F317L/V/I/C, or V299L mutation.
- **Nilotinib** – Avoid nilotinib for T315I, Y253H, E255K/V, F359V/C/I, or G250E mutation.
- **Ponatinib** – None known.
- **Imatinib** – Imatinib is ineffective for numerous *BCR-ABL1* mutations and is generally avoided for treatment of AP CML.

**Comorbidity-guided** — Certain comorbid conditions influence the choice of a TKI:

- **Heart disease** – We favor dasatinib or bosutinib (and avoid nilotinib) for patients with arrhythmias, coronary artery disease, or hyperglycemia.
- **Diabetes mellitus** – We favor dasatinib or bosutinib (and avoid nilotinib) for patients with arrhythmias, coronary artery disease, or hyperglycemia.
- **Pancreatitis** – We favor dasatinib (and avoid nilotinib and bosutinib) for patients with pancreatitis.
- **Lung diseases** – We favor nilotinib or bosutinib (and avoid dasatinib) for patients who have lung disease or are at risk for pleural effusion.

**Toxicity-guided** — We consider the following to be defining toxicities of second-generation (2G) TKIs:

- **Dasatinib** – Pleural effusion, pulmonary hypertension, prolonged QTc interval, platelet dysfunction
- **Nilotinib** – Coronary, cerebral, and peripheral vascular disease; prolonged QTc interval; hyperglycemia; pancreatitis

- **Bosutinib** – Diarrhea, abnormal liver function, rash, pancreatitis

**2G tyrosine kinase inhibitors** — Each 2G tyrosine kinase inhibitor (TKI) is associated with characteristic AEs, some of which may not be manifest for months or years.

In addition, all TKIs are associated with certain common AEs (eg, cytopenias, rash, nausea, muscle cramps, edema, diarrhea, fatigue) early in treatment, but most of the early AEs are modest and self-limited. Management of early AEs is discussed separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Managing toxicity'.)

**Dasatinib** — Dasatinib should be avoided in patients with lung disease or who at risk for pleural effusion. Treatment with dasatinib is associated with cytopenias, pleural effusion/fluid retention, QT prolongation, and bleeding ( table 3).

- **Administration** – For AP CML, dasatinib should be taken 140 mg once daily, with or without a meal; note that the recommended dose for AP CML differs from that in chronic phase (CP) CML [27]. Patients should be screened by electrocardiogram (EKG) for QTc interval at baseline, and hypokalemia or hypomagnesemia should be corrected before dasatinib administration.

Caution is advised in patients who require anticoagulants, drugs that inhibit platelet function, anti-arrhythmic agents, and medications or supplements that may prolong QTc ( table 4), as described separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Dasatinib').

- **Adverse effects** – Most AEs are mild, but patients may experience QTc prolongation, fluid retention (grade ≥3 in 4 percent), exacerbation of heart failure, pleural effusions, or bleeding from platelet dysfunction ( table 3) [27]. Severe central nervous system (CNS) and gastrointestinal hemorrhages have been reported in approximately 1 and 4 percent of patients, respectively; most cases were associated with severe thrombocytopenia, anticoagulants, and/or inhibitors of platelet function.
- **Outcomes** – In a trial that randomly assigned 317 patients with AP CML to dasatinib 140 mg once daily versus dasatinib 70 mg twice daily, response rates were comparable in both arms, but there was less toxicity with the single daily dose (ie, 20 versus 39 percent pleural effusions); most patients probably had transformed AP CML, because resistance or intolerance to imatinib was a study entry criterion [13]. With median follow-up of 15 months, rates of complete hematologic response (CHR), major cytogenetic response, and complete cytogenetic response (CCyR) were 50, 41, and 32 percent, respectively.

Treatment with dasatinib (70 mg twice daily) in 174 patients with AP CML (resistant or intolerant to imatinib) was associated with 64 percent major hematologic response (MHR), 45 percent CHR, and 32 percent CCyR after 14 month follow-up [28,29].

The US Food and Drug Administration (FDA) and European Medical Agency (EMA) labels recommend dasatinib 140 mg daily for AP CML [27].

**Nilotinib** — Nilotinib should be avoided in patients with heart disease or diabetes mellitus; it is the only TKI that must be taken twice daily and without food. Nilotinib is associated with cytopenias, hepatotoxicity, QTc prolongation, pancreatitis, and long-term cardiovascular complications ( table 3).

- **Administration** – Nilotinib 400 mg should be taken twice daily with water (approximately 12 hours apart); patients should avoid food  $\geq 2$  hours before and  $\geq 1$  hour after each dose. Note that the recommended dose for AP CML differs from that for CP CML [30].

Prior to initiating nilotinib treatment, serum lipase and amylase should be tested, baseline QTc interval measured, potassium and magnesium levels corrected, and other medications that may prolong QTc should be avoided.

- **Adverse effects** – Treatment with nilotinib has been associated with reversible and usually asymptomatic elevations in unconjugated bilirubin, lipase, and amylase. Most AEs are mild and self-limited, but pancreatitis and a low incidence of sudden deaths (possibly due to dysrhythmias) have been reported. Later effects include occlusive cardiac, cerebral, and peripheral artery disease; liver disease; and hyperglycemia.
- **Outcomes** – Treatment of 119 patients with AP CML with nilotinib (400 mg twice daily; escalated to 600 mg twice daily for inadequate response) was associated with 79 percent one-year overall survival (OS), 47 percent hematologic response (26 percent CHR), and 29 percent major cytogenetic response (MCyR; 16 percent CCyR) [31]. Grade  $\geq 3$  AEs included thrombocytopenia (35 percent), neutropenia (21 percent), and increased lipase (18 percent). With longer follow-up, 66 percent of patients who achieved MCyR sustained that response at 24 months [14]. Another study of 46 patients with imatinib-resistant AP CML reported similar rates of hematologic and cytogenetic response (33 and 22 percent, respectively) [32].

The US FDA [30] and EMA labels recommend nilotinib 400 mg twice daily for AP CML.

**Bosutinib** — Bosutinib should be avoided in patients with liver or kidney dysfunction, diarrhea, and heart failure. Treatment is associated with cytopenias, diarrhea, abnormal liver

function, and fluid retention.

- **Administration** – Bosutinib 500 mg once daily; note that the recommended dose for AP CML differs from that in CP CML [33].
- **Adverse effects** – Treatment is associated with diarrhea, nausea, and abdominal pain; the most common grade  $\geq 3$  AEs are diarrhea and abnormal liver function tests; there is a low incidence of cardiac and vascular AEs with bosutinib treatment with  $\geq 4$  year follow-up [34].
- **Outcomes** – Treatment of 72 patients with AP CML was associated with 57 percent overall hematologic response (31 percent CHR) by week 48; transformation to blast phase was reported in three patients [33]. In another report, 57 percent of 14 patients with AP CML attained or maintained baseline overall hematologic response and 40 percent attained or maintained MCyR [15].

The US FDA [33] and EMA recommend bosutinib 500 mg once daily for AP CML.

**Ponatinib** — Ponatinib, the only third-generation TKI, is associated with significant cardiovascular (CV) risks and complications, but it is the only TKI that is effective against the *BCR-ABL1* T315I kinase domain mutation. For patients with the T315I mutation who have substantial CV risk factors, other treatments may be preferred. (See 'Other treatments' below.)

- **Administration** – Ponatinib 45 mg should be taken once daily, with or without food. We do not reduce the ponatinib dose in patients with AP CML because it is uncertain if this will compromise response and/or reduce AEs in patients with AP CML. However, some experts reduce ponatinib to 30 mg for AP CML for *BCR-ABL1* <1 percent [35]. Many clinicians co-administer aspirin to mitigate CV complications of ponatinib, but this has not been shown to be beneficial.
- **Adverse effects** – Treatment with ponatinib is associated with CV AEs in more than one-fifth of patients, arterial thrombosis in 8 percent, and liver toxicity/failure is possible [36,37].
- **Outcomes** – A phase 2 study (PACE) reported outcomes with ponatinib in 83 patients with AP CML (resistant or intolerant to dasatinib or nilotinib), including patients with *BCR-ABL1* T315I mutations [38]. At five years, progression-free survival and OS were 22 and 49 percent, respectively. Other outcomes included MHR (61 percent), MCyR (49 percent), CCyR (31 percent), and major molecular response (MMR; 22 percent). In the PACE study, grade  $\geq 3$  thrombocytopenia, neutropenia, and anemia occurred in 44, 37, and 22 percent, respectively. The most common non-hematological toxicities were abdominal pain (42

percent), rash (38 percent), constipation (29 percent), dry skin (32 percent), and fatigue (38 percent) [38]. CV, cerebrovascular, and peripheral vascular events occurred in 7, 4, and 5 percent, respectively; most of these patients had at least one other risk factor (eg, hypertension, diabetes, hypercholesterolemia, obesity). Of the patients who continued ponatinib after a vascular event, 36 percent had subsequent events. Overall, severe AEs led to the discontinuation of therapy in 11 percent of patients; two patients died, including one death that was thought to be related to ponatinib (fungal pneumonia).

In another study, ponatinib treatment of 83 patients with AP CML was associated with 52 percent MHR (47 percent CHR) [36].

Ponatinib is approved for treatment of AP CML in which no other TKIs are indicated and for patients with *BCR-ABL1* T315I mutation by the US FDA [36] and the EMA.

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## OTHER TREATMENTS

Other treatments, alone or in combination with a tyrosine kinase inhibitor (TKI), are under investigation. Examples include:

- **Asciminib** – Asciminib is an allosteric inhibitor of BCR-ABL1 that specifically targets the ABL myristoyl pocket (STAMP). Asciminib is approved by the US Food and Drug Administration (FDA) for chronic phase (CP) CML that is resistant to ≥2 TKIs, including patients who harbor the *BCR-ABL1* T315I mutation.

The multicenter phase 3 ASCEMBL trial reported that asciminib had superior efficacy compared with bosutinib in patients with CP CML who had previously received ≥2 TKIs [39]. Patients were randomly assigned (2:1) to receive asciminib 40 mg twice daily versus bosutinib 500 mg once daily. Major molecular response (MMR) rate at week 24 was 26 percent with asciminib compared with 13 percent with bosutinib. Asciminib was also associated with fewer grade ≥3 adverse events (AE; 51 versus 61 percent, respectively) and fewer AEs leading to treatment discontinuation (6 versus 21 percent).

Treatment with asciminib in eight patients with AP CML reported complete hematologic response (CHR) in seven of eight patients and complete cytogenetic response (CCyR) and MMR in one of six patients [40]. Asciminib was active in patients who had resistance to or unacceptable AEs from TKIs, including patients with a T315I mutation in whom ponatinib had failed.

In another study, treatment with asciminib was associated with complete hematologic response (CHR) in seven of eight patients with accelerated phase (AP) CML and complete cytogenetic response (CCyR) and major molecular response (MMR) in one of six patients; asciminib was active in patients who had resistance to or unacceptable adverse effects (AEs) from TKIs, including patients with a T315I mutation in whom ponatinib had failed [40]. AEs were primarily asymptomatic elevations in lipase or amylase and grade <3 rash, fatigue, nausea, headache, or and arthralgias.

- **Omacetaxine mepesuccinate** (previously known as homoharringtonine) is an inhibitor of protein synthesis that is approved by the US FDA for treatment of AP CML in adults with resistance or intolerance to ≥2 TKIs [41]. Its use is generally limited to patients with the *BCR-ABL1* T315I mutation who have severe cardiovascular complications or risk factors that contraindicate treatment with ponatinib and are ineligible for allogeneic hematopoietic cell transplantation (HCT).

The recommended dose is 1.25 mg/m<sup>2</sup> subcutaneous injection twice daily for 14 days of a 28-day cycle for the induction phase and 1.25 mg/m<sup>2</sup> subcutaneous injection twice daily for 7 days of a 28-day cycle for maintenance [41].

Treatment of 41 patients with AP CML resistant to an initial TKI reported 11 percent CHR and one additional patient with <5 percent blasts in bone marrow [42]. Median time to response was two months and median duration of response was five months. Common toxicities included thrombocytopenia, neutropenia, anemia, infection, diarrhea, nausea, pyrexia, fatigue, asthenia, and arthralgia. The use of omacetaxine in patients with chronic phase disease is discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Omacetaxine'.)

- **Interferon** – Pegylated interferon is being studied in combination with 2G TKIs [43].
- **Others** – Azacitidine, decitabine, venetoclax, immunotherapies (eg, immune checkpoint blockade, leukemia-associated antigens, *BCR-ABL1* peptides, dendritic cell vaccines) and targeted agents (eg, aurora kinase inhibitors, farnesyl transferase inhibitors, JAK2 inhibitors) are being studied to deepen the molecular response to TKIs [44-50].

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## RESPONSE MONITORING

Response to a tyrosine kinase inhibitor (TKI) is evaluated by the timely achievement of hematologic, cytogenetic, and molecular milestones (table 5) [7]. Response is assessed by serial measurement in peripheral blood of *BCR-ABL1* by quantitative reverse transcriptase

polymerase chain reaction (qPCR). The qPCR assay should be standardized and have a sensitivity of  $\geq 4.5$ -log reduction from the baseline.

Optimal responses are:

- 3 months: *BCR-ABL1* (International Scale [IS])  $\leq 10$  percent and/or  $\leq 35$  percent Philadelphia chromosome-positive (Ph+) metaphase cells
- 6 months: *BCR-ABL1* IS  $\leq 1$  percent and/or 0 percent Ph+ cells
- 12 months: *BCR-ABL1* IS  $\leq 0.1$  percent

After *BCR-ABL1* is  $\leq 0.1$  percent, it should be measured every three months for the first two years and then every three to six months thereafter. At very low levels, the level of transcripts can fluctuate several-fold with successive tests. However, if there is a 1-log increase in *BCR-ABL1* after achieving a 3-log molecular response (MR3), this should be confirmed by repeating qPCR in one to three months. Further details and definitions of hematologic, cytogenetic, and molecular milestones are presented separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Response monitoring'.)

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## PROGNOSTIC FACTORS

Features that have been associated with outcomes in patients with accelerated phase (AP) CML include:

- **de novo versus transformed AP CML** – The distinction between de novo and transformed AP CML has prognostic importance, but also guides the approach to initial treatment. (See 'Treatment of de novo AP CML' above and 'Treatment of transformed AP CML' above.)
- **Major route additional chromosomal abnormalities (ACA) versus minor route ACA** – Major route ACAs (ie, second Philadelphia chromosome, trisomy 8, isochromosome 17q, trisomy 19) are associated with an adverse impact on survival [51-53]. The impact of minor route ACAs is currently less well-defined.
- **Increased blasts** – AP CML that was diagnosed because of increased blasts is associated with worse prognosis than AP CML that was diagnosed on the basis of other criteria (eg, basophils, ACAs) [1,54].
- **Rate of response to treatment** – Early response is predictive of long-term outcome. In a retrospective study, among 75 patients with AP CML, those who achieved *BCR-ABL1*  $< 10$

percent at three months had better overall survival and event-free survival (both 95 percent) compared to those who did not (79 and 59 percent, respectively) [55].

- **Molecular abnormalities** – Mutations of certain genes are found with high frequency in AP CML, but their prognostic importance is presently uncertain. As examples, single nucleotide variations (SNVs) and small insertions or deletions (indels) in *RUNX1* and *ASXL1*, plus *IKZF1* exon deletions; mutations of epigenetic regulators; and gene fusions involving *RUNX1*, *MLL* (*KMT2A*), and *CBFB* are common in AP CML [56,57].
- 

## 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".)

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## 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 5<sup>th</sup> to 6<sup>th</sup> 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 10<sup>th</sup> to 12<sup>th</sup> 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.)

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

## SUMMARY AND RECOMMENDATIONS

- **Chronic myeloid leukemia (CML)** is associated with t(9;22)(q34;q11), the Philadelphia chromosome (Ph), which creates the *BCR-ABL1* fusion gene and a constitutively active

tyrosine kinase that is sensitive to treatment with a BCR-ABL1 tyrosine kinase inhibitor (TKI). Up to 90 percent of patients with CML present in chronic phase (CP) CML, which is a relatively indolent disorder that responds well to TKIs; the remainder present with either accelerated phase (AP) CML or blast phase (BP; also called blast crisis) CML.

- **Diagnosis of AP CML** – We favor use of the World Health Organization (WHO) criteria to distinguish AP CML from CP CML and BP CML (see 'World Health Organization' above). WHO criteria for AP CML requires at least one of the following:

- **Blasts** – 10 to 19 percent myeloblasts in blood or bone marrow
- **Basophils** – ≥20 percent in blood
- **Thrombocytopenia** – Platelets persistently  $<100 \times 10^9/L$  (unrelated to therapy)
- **Additional chromosomal abnormalities (ACA)** – Major route ACAs in Ph+ cells at diagnosis (eg, second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 9), complex karyotype, or abnormalities of 3q26.2
- **New ACA while on treatment** – Development of any new ACA (ie, major route ACA or others) in Ph+ cells while treated with a TKI

Other models apply different diagnostic criteria, but we favor the WHO model because it is aligned with diagnostic criteria for other hematologic malignancies. (See 'Other models' above.)

- **Distinguishing de novo AP CML from transformed AP CML** has important implications for treatment and prognosis. (See 'de novo versus transformed AP' above.)
  - **de novo AP CML** refers to a patient whose initial presentation with CML is accelerated phase. Patients with de novo AP CML have not previously been treated with a TKI (ie, treatment-naïve), because this is the first presentation of their disease.
  - **Transformed AP CML** refers to a patient who previously presented with CP CML, but the disease progressed to AP (ie, transformed) during treatment with a TKI. Disease progression may be due to TKI-resistance from a *BCR-ABL1* mutation. Transformed AP CML generally has a less favorable prognosis than de novo AP CML.
- **Treatment of de novo AP CML** – For patients with de novo AP CML, we suggest treatment with a second-generation (2G) TKI, rather than allogeneic hematopoietic cell transplantation (HCT) or treatment with imatinib or ponatinib (**Grade 2C**) (algorithm 1)

because, compared with the other approaches, a 2G TKI provides the most favorable balance of efficacy and toxicity. (See 'Treatment of de novo AP CML' above.)

Selection of a 2G TKI for treatment of de novo AP CML is informed by comorbid conditions, toxicity profile, and *BCR-ABL1* mutation (if tested), as described above. (See 'Tyrosine kinase inhibitor selection' above.)

- **Treatment for transformed AP CML** is guided by the patient's suitability for allogeneic HCT (algorithm 2). Eligibility for transplantation depends on age, medical fitness, and an available suitable donor, as discussed separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)
  - **Transplant-eligible** – For transplant-eligible patients with transformed AP CML, we generally suggest allogeneic HCT rather than treatment with a TKI alone (**Grade 2C**), although we recognize that treatment must be individualized. Long-term disease control and possible cure with allogeneic HCT generally outweigh the adverse effects and risk of transplant-related mortality (TRM); by contrast, 2G TKIs or ponatinib have less potential for long-term disease control of transformed AP CML.
  - **Not transplant-eligible** – For patients with transformed AP CML who are not suitable for allogeneic HCT (eg, not medically-fit, no suitable donor, or the patient declines), we select a TKI according to *BCR-ABL1* mutation analysis, comorbid conditions, and toxicity profile. (See 'Not transplant-eligible' above.)
- **Selection of a TKI** – We select a TKI based on the following considerations (see 'Tyrosine kinase inhibitor selection' above):
  - **Mutation status** – For patients with transformed AP CML, we suggest *BCR-ABL1* mutation-guided TKI selection (**Grade 2C**). However, we generally do not perform mutation analysis for patients with de novo AP CML.
- Selection of a TKI based on *BCR-ABL1* mutations is presented above. (See 'Mutation-guided' above.)
- **Comorbid conditions** – Diabetes or disease of the heart, lung, liver, or pancreas may influence the choice of TKI, as described above. (See 'Comorbidity-guided' above.)
- **Toxicity profile** – Each TKI is associated with characteristic adverse effects (AEs) and selection may be influenced by toxicity profile. (See 'Toxicity-guided' above.)

- **Response monitoring** – Response to a TKI is evaluated by the timely achievement of hematologic, cytogenetic, and molecular milestones (table 5), as described above. (See 'Response monitoring' above.)

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Topic 4514 Version 35.0

## GRAPHICS

### Eastern Cooperative Oncology Group (ECOG) performance status

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

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Graphic 72901 Version 12.0

## Diagnostic criteria: accelerated phase of chronic myelogenous leukemia

MD Anderson*	Sokal et al <sup>¶</sup>	WHO <sup>Δ</sup>
PB blasts ≥15%	PB or BM blasts ≥5%	PB or BM blasts 10 to 19%
PB blasts + pro ≥30%		
PB baso ≥20%	PB basophils ≥20%	PB basophils ≥20%
Platelets <100,000/microL not related to therapy	Thrombocytopenia, not related to therapy	Platelets <100,000/microL, unrelated to therapy
Cytogenetic evolution	Cytogenetic evolution	Cytogenetic evolution or additional clonal chromosomal abnormalities in Ph+ cells at diagnosis that include "major route" abnormalities, complex karyotype, or abnormalities of 3q26.2
	Platelets >1 million/microL despite adequate therapy	Platelets >1,000,000/microL unresponsive to therapy
	Marrow collagen fibrosis	
	Anemia, unrelated to Rx	
	Progressive splenomegaly	Progressive splenomegaly and increasing WBC unresponsive to therapy
	WBC doubling time <5 days	
	Unexplained fever	
	Pelger-Huett-like neutrophils, nucleated RBCs, megakaryocyte fragments	

Examples of "major route" abnormalities defined by the WHO include second Ph, trisomy 8, isochromosome 17q, and trisomy 19. The WHO includes provisional response-to-tyrosine kinase inhibitor criteria for accelerated phase disease.

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WHO: World Health Organization; PB: peripheral blood; BM: bone marrow; pro: promyelocytes; baso: basophils; WBC: white blood cell count; RBC: red blood cells.

\* Kantarjian, HM, et al. Cancer 1988; 61:1441.

¶ Sokal, JE, et al. Semin Hematol 1988; 25:49.

Δ Arber, DA, et al. Blood 2016; 127:2391.

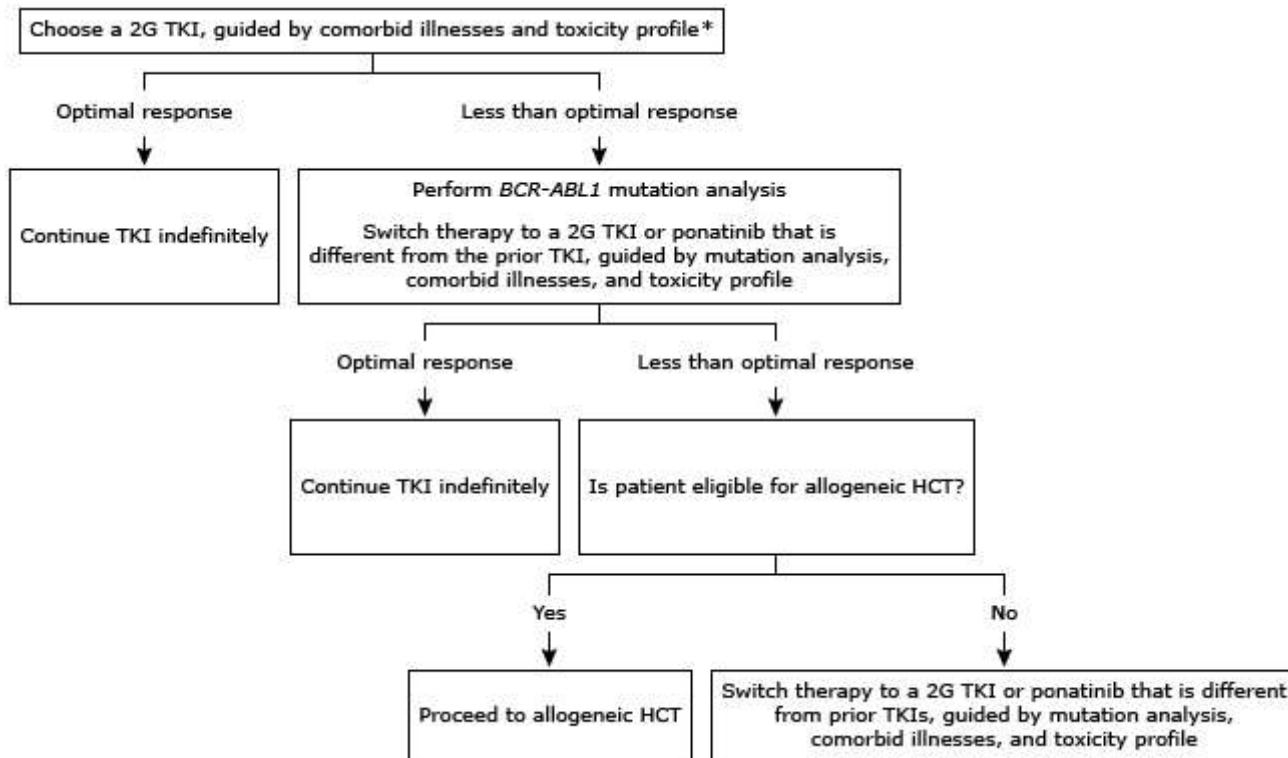
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*For each of the three sets of criteria, the accelerated phase of chronic myelogenous leukemia is diagnosed if one or more of the listed features is present. Adapted from O'Dwyer, ME, et al. Blood 2002; 100:1628.*

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Graphic 60902 Version 4.0

## Management of de novo accelerated phase chronic myeloid leukemia (ie, treatment-naïve AP CML)



This algorithm describes initial management of de novo CML AP; importantly, management of de novo AP CML differs from that of transformed AP CML (ie, AP CML that arose while the patient was receiving a TKI).

Refer to related UpToDate material for criteria for diagnosis of de novo CML AP, selection of a TKI, assessment of response to TKI, and eligibility for allogeneic HCT.

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AP CML: accelerated phase chronic myeloid leukemia; 2G TKI: second generation BCR-ABL1 tyrosine kinase inhibitor; HCT: hematopoietic cell transplantation.

\* If *BCR-ABL1* mutation analysis was performed, the choice of a TKI should also reflect mutation findings.

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## Comparison of tyrosine kinase inhibitors used for chronic myeloid leukemia

Agent	Dosing frequency and timing in relation to food	Dose adjustments for baseline kidney/liver dysfunction	Major toxicities	Other
Imatinib	Daily (or twice daily) with food	Yes (kidney, liver)	Bone marrow suppression; fluid retention/edema; gastrointestinal effects; heart failure; hepatotoxicity.	Longest record of safety data
Nilotinib	Twice daily without food	Yes (liver)	Bone marrow suppression; cardiovascular events; electrolyte imbalance; hepatotoxicity.  Black box warning: QT prolongation (screening required).	
Dasatinib	Daily with or without food	No	Bone marrow suppression; pleural/pericardial effusions; pulmonary arterial hypertension; QT prolongation; aspirin-like effect.	
Bosutinib	Daily with food	Yes (kidney, liver)	Bone marrow suppression; fluid retention/edema; gastrointestinal effects.	
Ponatinib	Daily with or without food	Yes (liver)	Bone marrow suppression; fluid retention/edema; gastrointestinal effects; heart failure; hypertension; pancreatitis; aspirin-	Active against <i>BCR::ABL1 T315I</i> mutation; limited long-term safety data

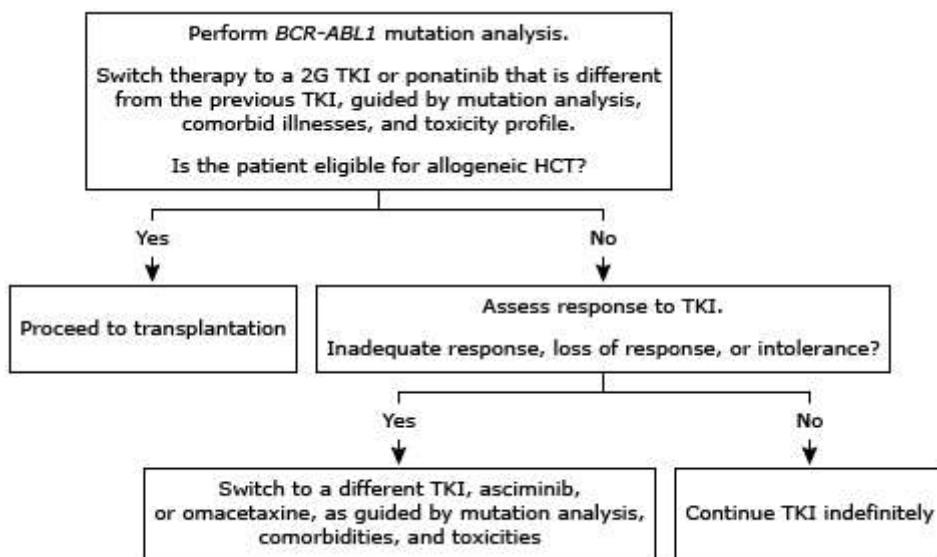
			like effect; arterial thrombosis.  Black box warning: cardiovascular events; hepatic toxicity.	
Asciminib	Daily or twice daily without food	No	Upper respiratory tract infections; musculoskeletal pain; fatigue; nausea; rash; and diarrhea.  Hypertriglyceridemia; cytopenias; elevated creatine kinase; hepatotoxicity; pancreatitis.	Active against <i>BCR::ABL1</i> T315I mutation; limited long-term safety data

The table provides general guidance regarding the administration and toxicities of these tyrosine kinase inhibitors. Further details are available within the package inserts and UpToDate topics.

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Graphic 89930 Version 4.0

# Management of transformed accelerated phase chronic myeloid leukemia (AP CML)



This algorithm describes management of transformed AP CML (ie, AP CML that arose while the patient was receiving a TKI); importantly, management of transformed AP CML differs from that of de novo CML (ie, patients whose initial presentation is AP CML and who have not received prior TKI therapy).

Refer to related UpToDate material for diagnostic criteria for transformed CML AP, selection of a TKI, and eligibility for allogeneic HCT.

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CML: chronic myeloid leukemia; AP: accelerated phase; 2G TKI: second generation BCR-ABL1 tyrosine kinase inhibitor; HCT: hematopoietic cell transplantation.

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Graphic 131961 Version 1.0

## Some reported causes and potentiators of the long QT syndrome

<b>Congenital</b>																			
<ul style="list-style-type: none"> <li>▪ Jervell and Lange-Nielsen syndrome (including "channelopathies")</li> <li>▪ Romano-Ward syndrome</li> <li>▪ Idiopathic</li> </ul>																			
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■ Certinib	■ Escitalopram	■ Levofloxacin (systemic)	■ Ribociclib
■ Chloroquine	■ Etelcalcetide	■ Lofexidine	■ Risperidone
■ Citalopram	■ Fexinidazole	■ Meglumine antimoniate	■ Saquinavir
■ Clarithromycin	■ Flecainide	■ Midostaurin	■ Sevoflurane
■ Clofazimine	■ Floxuridine	■ Moxifloxacin	■ Sparfloxacin¶
■ Clomipramine¥	■ Fluconazole	■ Nilotinib	■ Sunitinib
■ Clozapine	■ Fluorouracil (systemic)	■ Olanzapine	■ Tegafur¶
■ Crizotinib	■ Flupentixol¶	■ Ondansetron (IV > oral)	■ Terbutaline
■ Dabrafenib	■ Gabobenate dimeglumine	■ Osimertinib	■ Thioridazine
■ Dasatinib	■ Gemifloxacin¶	■ Oxytocin	■ Toremifene
■ Deslurane	■ Gilteritinib	■ Pazopanib	■ Vemurafenib
■ Domperidone¶	■ Halofantrine	■ Pentamidine	■ Voriconazole
■ Doxepin¥	■ Haloperidol (oral)	■ Pilsicainide◊	
■ Doxifluridine¶	■ Imipramine¥	■ Pimozone	
		■ Piperaquine	
		■ Probucol◊	

### Low risk‡

■ Albuterol	■ Fingolimod	■ Mequitazine	■ Ranolazine (due to bradycardia)
■ Alfuzosin	■ Fluoxetine	■ Methotrimeprazine	■ Relugolix
■ Amisulpride (IV)§	■ Fluphenazine	■ Metoclopramide (rare reports)	■ Rilpivirine
■ Amitriptyline¥	■ Formoterol	■ Metronidazole (systemic)	■ Romidepsin
■ Anagrelide	■ Foscarnet	■ Mifepristone	■ Roxithromycin
■ Apomorphine	■ Gadofosveset	■ Mirtazapine	■ Salmeterol
■ Arformoterol	■ Glasdegib	■ Mizolastine	■ Sertraline
■ Artemether- lumefantrine	■ Goserelin	■ Nelfinavir	■ Siponimod
■ Asenapine	■ Granisetron	■ Norfloxacin	■ Solifenacin
■ Atomoxetine	■ Hydroxychloroquine (rare reports)	■ Nortriptyline¥	■ Sorafenib
■ Benperidol	■ Hydroxyzine	■ Ofloxacin (systemic)	■ Sulpiride
■ Bilastine¶	■ Iloperidone	■ Olodaterol	■ Tacrolimus (systemic)
■ Bosutinib	■ Indacaterol	■ Osilodrostat	■ Tamoxifen
■ Bromperidol	■ Itraconazole	■ Oxaliplatin	■ Telavancin
■ Buprenorphine†	■ Ketoconazole (systemic)	■ OzanimodΔΔ	■ Telithromycin
■ Buserelin	■ Lacidipine	■ Pacritinib	■ Teneligliptin
■ Ciprofloxacin (Systemic)	■ Lapatinib	■ Paliperidone	■ Tetrabenazine
■ Cocaine (Topical)	■ Lefamulin	■ Panobinostat	■ Trazodone
■ Degarelix			■ Triclabendazole

■ Desipramine <sup>¥</sup>	■ Leuprolide	■ Pasireotide	■ Triptorelin
■ Deutetrabenazine	■ Leuprolide-norethindrone	■ Pefloxacin	■ Tropisetron <sup>¶</sup>
■ Dexmedetomidine**	■ Levalbuterol	■ Periciazine <sup>¶</sup>	■ Vardenafil
■ Dolasetron	■ Levomethadone	■ Pimavanserin	■ Vilanterol
■ Donepezil	■ Lithium	■ Pipamperone	■ Vinflunine
■ Efavirenz	■ Loperamide <sup>¶¶</sup> in overdose	■ Pitolisant	■ Voclosporin
■ Eliglustat	■ Lopinavir	■ Ponesimod	■ Vorinostat
■ Eribulin	■ Macimorelin	■ Primaquine	■ Zuclopentixol
■ Ezogabine	■ Mefloquine	■ Promazine	
		■ Radotinib	

This is not a complete list of all corrected QT interval (QTc)-prolonging drugs and does not include drugs with either a minor degree or isolated association(s) with QTc prolongation that appear to be safe in most patients but may need to be avoided in patients with congenital long QT syndrome depending upon clinical circumstances. A more complete list of such drugs is available at the CredibleMeds website. For clinical use and precautions related to medications and drug interactions, refer to the UpToDate topic review of acquired long QT syndrome discussion of medications and the Lexicomp drug interactions tool.

AV: atrioventricular; IV: intravenous; QTc: rate-corrected QT interval on the electrocardiogram.

\* Classifications provided by Lexicomp according to US Food & Drug Administration guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers; Guidance for Industry US Food and Drug Administration, June 2017 (revision 2) available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073161.pdf> as updated August 8, 2023 (<https://www.fda.gov/media/170814/download>) with additional data from CredibleMeds QT drugs list<sup>[1,2]</sup>. The use of other classification criteria may lead to some agents being classified differently by other sources.

¶ Not available in the United States.

Δ In contrast with other class III antiarrhythmic drugs, amiodarone is rarely associated with torsades de pointes; refer to accompanying text within UpToDate topic reviews of acquired long QT syndrome.

◊ Withdrawn from market in most countries due to adverse cardiovascular effects.

§ IV amisulpride antiemetic use is associated with less QTc prolongation than the higher doses administered orally as an antipsychotic.

¥ Some other cyclic antidepressants (ie, amoxapine, maprotiline, protriptyline, trimipramine) may also prolong the QT interval, but data are insufficient to identify level of risk with confidence; refer to UpToDate content on cyclic antidepressant pharmacology, administration, and side effects.

‡ The "low risk" category includes drugs with limited evidence of clinically significant QTc prolongation or TdP risk; many of these drugs have label warnings regarding possible QTc effects or

recommendations to avoid use or increase ECG monitoring when combined with other QTc prolonging drugs.

† Rarely associated with significant QTc prolongation at usual doses for treatment of opioid use disorder, making buprenorphine a suitable alternative for patients with methadone-associated QTc prolongation. Refer to UpToDate clinical topic reviews.

\*\* The United States FDA labeling for the sublingual preparation of dexmedetomidine warns against use in patients at elevated risk for QTc prolongation. Both intravenous (ie, sedative) and sublingual formulations of dexmedetomidine have a low risk of QTc prolongation and have **not** been implicated in TdP.

¶¶ Over-the-counter; available without a prescription.

ΔΔ Not associated with significant QTc prolongation in healthy persons. Refer to UpToDate clinical topic for potential adverse cardiovascular (CV) effects in patients with CV disease.

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*Data from:*

1. Lexicomp Online. Copyright ©1978-2023 Lexicomp, Inc. All Rights Reserved.
  2. CredibleMeds QT drugs list website sponsored by Science Foundation of the University of Arizona. Available at <http://crediblemed.org/>.
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Graphic 57431 Version 147.0

## Definition of the response to tyrosine kinase inhibitors as first-line treatment of chronic myeloid leukemia

	<b>Optimal</b>	<b>Warning</b>	<b>Failure</b>
<b>Baseline</b>	NA	High risk or CCA/Ph+, major route	NA
<b>Three months</b>	BCR-ABL1 ≤10 percent and/or Ph+ ≤35 percent	BCR-ABL1 >10 percent and/or Ph+ 36 to 95 percent	Non-CHR and/or Ph+ >95 percent
<b>Six months</b>	BCR-ABL1 <1 percent and/or Ph+ 0	BCR-ABL1 1 to 10 percent and/or Ph+ 1 to 35 percent	BCR-ABL1 >10 percent and/or Ph+ >35 percent
<b>12 months</b>	BCR-ABL1 ≤0.1 percent	BCR-ABL1 >0.1 to 1 percent	BCR-ABL1 >1 percent and/or Ph+ >0
<b>Then, and at any time</b>	BCR-ABL1 ≤0.1 percent	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Confirmed loss of MMR* Mutations CCA/Ph+

The definitions are the same for patients in chronic phase, accelerated phase, and blast crisis and apply also to second-line treatment, when first-line treatment was changed for intolerance. The response can be assessed with either a molecular or a cytogenetic test, but both are recommended whenever possible. Cutoff values have been used to define the boundaries between optimal and warning, and between warning and failures. Because cutoff values are subjected to fluctuations, in case of cytogenetic or molecular data close to the indicated values, a repetition of the tests is recommended. After 12 months, if an MMR is achieved, the response can be assessed by real quantitative polymerase chain reaction (RQ-PCR) every three to six months, and cytogenetics is required only in case of failure or if standardized molecular testing is not available. Note that MMR (MR<sup>3.0</sup> or better) is optimal for survival, but that a deeper response is likely to be required for a successful discontinuation of treatment.

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NA: not applicable; MMR: BCR-ABL1 ≤0.1 percent = MR<sup>3.0</sup> or better; CCA/Ph+: clonal chromosome abnormalities in Ph+ cells; CCA/Ph-: clonal chromosome abnormalities in Ph- cells; CHR: complete hematologic response; CCyR: complete cytogenetic response; MMR: major molecular response.

\* In two consecutive tests, of which one with a BCR-ABL1 transcripts level ≥1 percent.



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