



Initial treatment of chronic myeloid leukemia in chronic phase

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with the Philadelphia chromosome t(9;22)(q34;q11) and the *BCR::ABL1* fusion gene, which produces a constitutively active *BCR::ABL1* tyrosine kinase. Most patients present in chronic phase (CP) CML, which is typically manifest as leukocytosis and immature myeloid cells in peripheral blood, with or without anemia, thrombocytopenia, constitutional symptoms, splenomegaly, and/or bleeding. CP CML can progress from a relatively indolent disorder to the more aggressive disorders, accelerated phase or blast crisis.

The initial treatment of CP CML will be discussed here.

Clinical presentation and diagnosis of CML, treatment of relapsed/resistant CML, and management of accelerated phase and blast crisis are discussed separately.

- (See "Clinical manifestations and diagnosis of chronic myeloid leukemia".)
 - (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)
 - (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment".)
 - (See "Treatment of chronic myeloid leukemia in blast crisis".)
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GOALS OF CARE

The goals of care for patients with CP CML are:

- For all patients for management of chronic phase CML are to achieve clinical remission, maintain long-term disease control, and avoid disease progression to accelerated phase or blast crisis, while optimizing quality of life by limiting treatment-related toxicity.
- For patients who achieve a sustained and deep molecular remission, a trial of discontinuation of therapy to achieve a treatment-free remission (TFR) is a long-term goal of management. Criteria for considering a trial of tyrosine kinase inhibitor (TKI) discontinuation are described below. (See 'TKI discontinuation for TFR' below.)

Milestones for hematologic, cytogenetic, and molecular responses (table 1), which are surrogates of disease control, are described below. (See 'Treatment response' below.)

PRETREATMENT EVALUATION

Clinical and laboratory evaluation

- **Clinical** – History should determine performance status (table 2) and identify medical comorbidities, current medications, cardiovascular risk factors, and insurance status. Physical examination must include documentation of blood pressure and measurements of liver and spleen size (below the costal margin) by palpation.
- **Laboratory studies**
 - Complete blood count (CBC) with differential count.
 - Serum chemistries – Electrolytes, renal and liver function tests, uric acid, lactate dehydrogenase.
 - Hepatitis B panel – HBsAg, HBsAb, anti-HBc IgM and IgG antibodies; reactivation of hepatitis B in association with tyrosine kinase inhibitor (TKI) therapy has been described in case reports, but the risk is not well-defined.
 - Electrocardiogram (EKG) to measure baseline QTc interval; some clinicians obtain an EKG only in patients who will be treated with nilotinib or dasatinib. (See 'Society guideline links' below.)
- **BCR::ABL1** – Quantitative reverse-transcription polymerase chain reaction (qRT-PCR) for *BCR::ABL1* should be performed prior to initiation of a TKI, to establish that quantifiable transcripts can be identified using a standard primer pair and to enable molecular monitoring of response. (See 'Treatment response' below.)
- **Bone marrow examination** – Bone marrow should be examined for morphology (eg, fibrosis, blast count) and cytogenetics as a baseline measure. Some experts consider that bone marrow examination is not required if CP CML was diagnosed on the basis of cytogenetics and polymerase chain reaction (PCR) from peripheral blood. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Diagnosis'.)

Patients who are found to have additional cytogenetic abnormalities (ie, cytogenetic abnormalities in addition to t(9;22)) are discussed below. (See 'Additional chromosomal abnormalities' below.)

CML risk score — CML risk score, using one of the validated CML scoring systems (table 3), should be calculated prior to treatment initiation. The preferred scoring system varies by practitioner, but any one of the following is acceptable:

- Sokal (calculator 1) [1]
- Euro (Hasford) [2]

- EUTOS [3]
- ELTS (EUTOS long-term survival score) (calculator 2) [4]

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 was derived from survival data that reflect treatment of CML with TKIs, and it provides the best discrimination for the probability of CML-specific death [4,5]. The other models were derived from data sets that included some patients who were treated before the routine use of TKIs.

Use of clinical scoring systems for defining prognosis in CML is described separately. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Scoring systems'.)

RATIONALE FOR TKI TREATMENT

With the exception of CML diagnosed during pregnancy, we recommend a BCR::ABL1 tyrosine kinase inhibitor (TKI) for initial treatment of all patients with CP CML, based on superior treatment outcomes and modest toxicity compared with other treatments (eg, cytotoxic agents, interferons, hematopoietic cell transplantation) [6].

All BCR::ABL1 TKIs are associated with similar rates of hematologic, cytogenetic, and molecular remissions and, compared with age- and sex-matched control populations, long-term survival of patients with CP CML is normal or near-normal [7-11]. Selection of a BCR::ABL1 TKI is described below. (See 'Choosing a TKI' below.)

Management of CP CML in pregnancy is discussed below. (See 'Pregnancy' below.)

CHOOSING A TKI

We stratify selection of a BCR::ABL1 TKI according to the CML risk score and the goal of achieving a treatment-free remission (TFR) (algorithm 1). The choice of a particular TKI for initial treatment must also consider the side effect profile (table 4), comorbid illnesses, availability, cost, and patient preference.

Our approach to choosing a BCR::ABL1 TKI for initial treatment of CP CML follows:

- **CML risk score** – Determination of the CML risk score using one of the validated CML scoring systems (table 3) is described above. (See 'CML risk score' above.)

Selection of a TKI based on CML risk score is described below. (See 'High-risk CML' below and 'Low- or intermediate-risk CML' below.)

- **Treatment-free remission** – For patients who assign a high priority to achieving TFR, selection of a TKI is described below. (See 'TFR is an important goal' below.)

All BCR::ABL1 TKIs are highly effective for initial treatment of CP CML. There are no significant differences in overall survival (OS) between patients who initiate treatment with imatinib versus a second-generation (2G)

TKI, based on long-term outcomes data from phase 3 trials [12-15]. Compared with imatinib, 2G TKIs generally achieve faster and deeper remissions and are associated with lower rates of progression to advanced phase CML. Details of the efficacy and adverse effects (AEs) of individual TKIs are presented below. (See 'Individual TKIs' below.)

In a meta-analysis of eight randomized trials of TKIs in CP CML, imatinib and 2G TKIs achieved comparable rates of OS and progression-free survival (PFS), but 2G TKIs were associated with higher rates of complete cytogenetic response (relative risk [RR] 0.72; 95% CI 0.60-0.85) and major molecular response (ie, *BCR::ABL1* <0.1 percent; RR 0.76; 95% CI 0.63-0.91) [16]. The meta-analysis also reported that disease progression was lower with 2G TKIs than with imatinib (0.8 versus 3.0 percent, respectively; RR 0.35; 95% CI 0.18-0.72). However, this conclusion was strongly influenced by one trial (ENESTnd) among the six that reported rates of disease progression to accelerated phase/blast crisis (AP/BC); methodologic aspects that may have affected the rate of progression in ENESTnd are discussed below [13]. (See 'Nilotinib' below.)

In all randomized trials, approximately one-third of patients switched to alternative TKIs due to toxicity, suboptimal response, or other reasons. Treatment, toxicities, and outcomes with individual TKIs used as initial therapy for CP CML and comparisons of 2G TKIs with imatinib are presented below. (See 'Individual TKIs' below.)

High-risk CML — For patients with high-risk CP CML, we suggest treatment with a 2G TKI (eg, nilotinib, dasatinib, bosutinib), when available, rather than imatinib (algorithm 1). Progression to AP/BC is a concern in patients with high-risk CML and, compared with imatinib, 2G TKIs may be associated with lower rates of disease progression. Nevertheless, imatinib and 2G TKIs achieve comparable rates of OS, PFS, and AEs.

None of the 2G TKIs has proven to be superior in this setting. The choice of an individual 2G TKI must consider the toxicity profile, comorbid conditions, availability, cost, and patient preference. Selection of a TKI based on AEs and comorbid conditions is discussed below. (See 'Toxicities' below.)

Low- or intermediate-risk CML — For patients with low-risk or intermediate-risk CP CML, the choice of a TKI is influenced by the importance assigned to achievement of a TFR, as described below.

TFR is an important goal — For patients with low- or intermediate-risk CP CML who consider a TFR an important goal, we suggest a 2G TKI rather than imatinib (algorithm 1), because 2G TKIs are associated with faster and deeper responses and are more likely to enable a trial of TKI discontinuation. Eligibility criteria for a trial of TKI discontinuation and outcomes are described below. (See 'TKI discontinuation for TFR' below.)

The choice of a TKI must also consider the side effect profile (table 4), comorbid illnesses, availability, cost, and patient preference. (See 'Toxicities' below.)

Approximately half of patients who discontinue a TKI remain in a long-term TFR. A sustained TFR might be expected in 10 to 15 percent of patients with newly diagnosed CML (ie, half of the approximately one-third of patients who achieve a sustained, deep molecular remission). There are no prospective data comparing different TKIs for achievement of TFR, but as a hypothetical example, in the ENESTnd study, among 100 patients who start nilotinib, 63 would be expected to achieve MR4.5 by five years and half of them (31

patients) would likely have a successful TFR; by contrast, among 100 patients treated with imatinib, 42 would be expected to achieve MR4 by year 5 and 21 patients would likely achieve a successful TFR [17].

TFR is not important — For patients who do not consider achieving a TFR a high priority, treatment with imatinib or a 2G TKI is acceptable (algorithm 1). The choice of a TKI must consider the side effect profile (table 4), comorbid illnesses, availability, cost, and patient preference. (See 'Toxicities' below.)

Imatinib and 2G TKIs (eg, nilotinib, dasatinib, bosutinib) achieve comparable rates of OS, PFS, and AEs [16]. Some clinicians favor imatinib because it has the longest record of safety and efficacy, is most widely available, and is generally least expensive. Others favor 2G TKIs because they generally achieve faster and deeper molecular responses than imatinib. (See 'Individual TKIs' below.)

Toxicities — All TKIs are associated with certain common AEs (eg, cytopenias, rash, nausea, muscle cramps, edema, diarrhea, fatigue) early in the course of treatment. Most of these early AEs are modest and self-limited, or can be managed as discussed below. (See 'Common early toxicities' below.)

Each TKI is also associated with particular AEs, some of which may not be manifest for months or years (table 4). We consider the following to be such defining toxicities:

- **Imatinib** – Muscle cramps, fatigue, edema, nausea, diarrhea.
- **Nilotinib** – Coronary, cerebral, and peripheral vascular disease; prolonged QTc interval; hyperglycemia; pancreatitis.
- **Dasatinib** – Pleural effusion, pulmonary hypertension, prolonged QTc interval, platelet dysfunction.
- **Bosutinib** – Diarrhea, abnormal liver function, rash, pancreatitis.

As examples of how we consider comorbidities and AEs in selecting a TKI (algorithm 1):

- For patients with arrhythmias, coronary artery disease, or hyperglycemia, we favor imatinib, bosutinib, or dasatinib.
- For patients with a history of pancreatitis we try to avoid nilotinib and bosutinib.
- For patients with a history of lung disease or at risk for pleural effusion, we favor imatinib, nilotinib, or bosutinib.

In randomized trials of CP CML, approximately one-third of patients switched to alternative TKIs for a variety of reasons, including toxicity and suboptimal response. Treatment, toxicities, and outcomes with individual TKIs used as initial therapy for CP CML and comparisons of 2G TKIs with imatinib are presented below. (See 'Individual TKIs' below.)

INDIVIDUAL TKIS

Several tyrosine kinase inhibitors (TKI) are approved for initial treatment of CP CML [18]. Imatinib was the first commercially available TKI to be approved by the US Food and Drug Administration (FDA) and by the

European Medicines Administration (EMA) for initial treatment of CML. Second-generation (2G) TKIs (ie, nilotinib, dasatinib, bosutinib) were initially approved for treatment of CML after disease resistance or toxicity with imatinib, but each was subsequently approved by the FDA and EMA for initial treatment of CML based on comparisons with imatinib in randomized trials.

Imatinib — Imatinib has the longest record of safety and efficacy among TKIs, is available as a generic medication, and is generally less expensive than 2G TKIs. Long-term outcomes with imatinib are comparable to those with 2G TKIs, but imatinib may be slower to achieve cytogenetic and molecular responses [16]. Imatinib is associated with cytopenias and edema and it causes substantial fluid retention in some patients. We generally avoid imatinib in patients with a history of significant fluid retention or nausea, and we favor 2G TKIs for patients with high-risk CML and for those who assign high priority to achieving a treatment-free remission (TFR), as discussed above. (See 'High-risk CML' above and 'TFR is an important goal' above.)

- **Initial treatment** – We suggest initial treatment with imatinib 400 mg once daily with a meal and a large glass of water; tablets can also be dispersed in water or apple juice [19]. The initial dose of imatinib should be adjusted for liver or renal impairment, and concurrent use of strong CYP3A4 inducers should be avoided.
- **Toxicity** – The most common adverse events (AE) with imatinib, such as cytopenias, edema, nausea, diarrhea, rash, and muscle cramps (table 4), are generally mild; grade 3 to 4 AEs are reported in ≤5 percent of patients [19]. Imatinib may be associated with hypophosphatemia and decreased bone mineral density [20,21].

The dose should be adjusted for changes in liver and kidney function and the patient should be monitored for fluid retention, particularly in older patients and in those with cardiovascular (CV) comorbidities [19]. Monitoring, dose adjustment, and other management of common early toxicities, cytopenias, and other AEs are discussed below. (See 'Monitoring toxicity' below and 'Managing toxicity' below.)

- **Outcomes** – In CP CML, imatinib achieves long-term outcomes that are comparable to those with 2G TKIs, but 2G TKIs generally achieve faster and/or deeper cytogenetic and molecular responses [16]. In patients with CP CML, imatinib achieves complete hematologic response (CHR), complete cytogenetic response (CCyR), and major molecular response (MMR; ie, >3-log reduction in *BCR::ABL1* transcripts by the International Scale [IS]) (table 1) in >95 percent, >75 percent, and nearly 60 percent, respectively [22]. Definitions of hematologic, cytogenetic, and molecular responses are described below. (See 'Definitions of response' below.)

Phase 3 trials that included imatinib as initial treatment of CP CML include:

- The IRIS (International Randomized Study of Interferon [IFN] and STI571 [imatinib]) trial reported that imatinib is superior to IFN alfa plus cytarabine [22]. In the IRIS trial, 1106 patients with newly diagnosed CP CML were randomly assigned to imatinib (400 mg once daily) versus IFN alfa (5 million units/m² daily) plus cytarabine (20 mg/m² daily for 10 days/month). After 18 months, compared with IFN alfa plus cytarabine, imatinib achieved superior CHR (97 versus 69 percent), CCyR (76 versus 15 percent), MMR (39 versus 2 percent), and progression-free survival (PFS; 97 versus 92 percent).

Imatinib was also associated with better quality of life and was better tolerated than IFN alfa plus cytarabine [22-25]. After 10 year follow-up of 204 patients, 93 percent had MMR and 63 percent had MR 4.5 (>4.5-log reduction in *BCR::ABL1*) [12]. Although 10-year overall survival (OS) in this trial was 84 percent, imatinib did not achieve a survival advantage because approximately 90 percent of patients assigned to receive IFN alfa plus cytarabine ultimately crossed over to imatinib [12,26-28].

- The CML-IV trial evaluated various imatinib doses and combinations with other agents [8]. In CML-IV, 1551 patients were randomly assigned to imatinib 400 mg per day, imatinib 800 mg per day, or imatinib 400 mg daily plus either IFN alfa or cytarabine. After 10 years, PFS and OS were 80 and 82 percent, respectively, and there were no survival differences among treatment arms. Other studies of imatinib in CP CML reported similar clinical outcomes and toxicities [29-40].

Higher doses of imatinib (eg, 600 mg, 800 mg) or a combination of imatinib with other agents (eg, cytarabine, interferon alfa) can achieve earlier cytogenetic and molecular milestones, but higher doses are associated with more toxicity and do not improve OS [8,41-49].

Prospective trials that compared imatinib to 2G TKIs in CP CML are described below. (See 'Nilotinib' below and 'Dasatinib' below and 'Bosutinib' below.)

Second-generation (2G) TKIs

Nilotinib — Nilotinib is a 2G TKI and 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 CV complications (table 4). As discussed below, nilotinib may be associated with lower rates of progression to accelerated phase (AP) or blast crisis (BC) than imatinib.

- **Initial treatment** – We suggest initial treatment with nilotinib 300 mg twice daily (approximately 12 hours apart) with water; patients should avoid food ≥2 hours before and ≥1 hour after taking each dose [50]. Lipase and amylase should be tested prior to treatment. Patients should be screened by electrocardiogram (EKG) for QTc interval at baseline, potassium and magnesium levels should be corrected, and other medications that may prolong QTc interval (table 5) should be avoided. Caution is advised for patients with poorly controlled diabetes, liver disease, pancreatitis, or substantial CV risk factors.
- **Toxicity** – Most AEs (table 4) are mild and self-limited, but pancreatitis and a low incidence of sudden deaths (which may be related to ventricular repolarization abnormalities) have been reported [50]. Later effects of nilotinib therapy include occlusive cardiac, cerebral, and peripheral artery disease; liver disease; and hyperglycemia.

The dose of nilotinib should be adjusted for prolongation of QTc interval, elevation of lipase/amylase, or changes in liver and kidney function [50]. Monitoring, dose adjustment, and other management for common early toxicities, cytopenias, changes in lipase/amylase and liver function tests, prolongation of QTc interval, and other cardiovascular events are discussed below. (See 'Monitoring toxicity' below and 'Managing toxicity' below.)

- **Outcomes** – Treatment with nilotinib 300 mg twice daily, when directly compared with imatinib, was associated with comparable PFS and OS (approximately 95 percent OS after two years), higher rates of molecular responses, more CV events, and lower rates of progression to AP/BC in one study (ENESTnd).

The following trials directly compared nilotinib with imatinib:

- In ENESTnd, 846 previously untreated patients with CP CML were randomly assigned to nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, or imatinib 400 mg daily [13,51-54]. Compared with imatinib, nilotinib 300 mg twice daily (the approved dose) was associated with comparable five-year OS, PFS, and event-free survival (EFS). The estimated rate of progression to AP/BC at five years was lower with nilotinib than imatinib. Compared with imatinib (33 patients progressed to AP/BC), progression was reported in 12 patients taking nilotinib 300 mg twice daily (HR 0.46; 95% CI 0.22-0.99) and 9 patients taking nilotinib 400 mg twice daily (HR 0.28; 95% CI 0.11-0.68) [13]. Most progression events occurred in patients with intermediate- or high-risk disease. Nilotinib 400 mg twice daily was superior to imatinib with regard to OS, PFS, EFS, and progression, but this dose was associated with unacceptable levels of CV toxicity [13,51-54]. More than half of all patients treated with nilotinib (at either dose level) achieved MR 4.5, compared with less than one-third with imatinib.

In ENESTnd, the incidence of grade ≥ 3 AEs and toxicity that led to treatment discontinuation were comparable between nilotinib 300 mg twice daily and imatinib [13]. Compared with imatinib, both dose levels of nilotinib were associated with less fluid retention, pleural effusion, pericardial effusion, pulmonary edema, and grade ≥ 3 neutropenia. However, all-grade CV events (eg, ischemic heart disease, ischemic CV events, peripheral artery disease) were reported in 7.5 percent, 13.4 percent, and 2.1 percent of patients in the nilotinib 300 mg, nilotinib 400 mg, and imatinib arms, respectively. With five years of follow-up, new or worsening grade ≥ 3 elevations of lipase, glucose, and liver enzymes were more common in either nilotinib arm than with imatinib. Grade ≥ 3 symptomatic prolongation of QTc was reported in 0.7 and 1.4 percent of patients treated with nilotinib 300 mg or 400 mg.

- In ENESTchina, 267 Chinese patients with newly diagnosed CP CML were randomly assigned to nilotinib (300 mg twice daily) versus imatinib (400 mg daily) [55]. Nilotinib achieved higher MMR at 12 months (52 versus 28 percent) and similar rates of both CCyR (84 versus 87 percent) and freedom from progression (95 percent each) at 24 months [55]. Toxicities were similar to those reported in ENESTnd.

Dasatinib — Dasatinib is a 2G TKI that is associated with cytopenias, pleural effusions, other fluid retention, QT prolongation, and bleeding (table 4). It should not be given to patients with hypokalemia, hypomagnesemia, or who have or may develop prolongation of the QTc interval, and we generally avoid dasatinib in patients with a bleeding history, pleural effusion, and heart failure. Caution is advised when it is given with certain medications (described below).

- **Initial treatment** – We suggest initial treatment with dasatinib 100 mg once daily, with or without a meal; tablets should not be crushed or cut [56]. Patients should be screened by EKG for QTc interval at baseline, and hypokalemia or hypomagnesemia should be corrected before administration of dasatinib. No initial dose adjustment is required for patients with liver or kidney impairment, but caution is

advised in patients who require anticoagulants, medications that inhibit platelet function, anti-arrhythmic medicines or other products that may lead to QTc prolongation (table 5), strong CYP3A4 inducers or inhibitors (table 6), St. John's wort, antacids, H2 antihistamines, and proton pump inhibitors (PPIs).

- **Toxicity** – Most AEs (table 4) are mild and self-limited. However, patients may experience QTc prolongation, fluid retention (grade ≥3 in approximately 4 percent), exacerbation of congestive heart failure, or significant bleeding [56]. Severe and potentially fatal central nervous system (CNS) and gastrointestinal hemorrhages have been reported in approximately 1 and 4 percent of patients, respectively; most bleeding events were associated with severe thrombocytopenia, anticoagulants, and/or inhibitors of platelet function.

The dose of dasatinib should be adjusted for prolongation of QTc interval. Patients who develop dyspnea, dry cough, or other findings suggestive of pleural effusion should be evaluated with a chest radiograph; some patients develop a patchy interstitial pneumonitis with fever that can mimic an infection and rare cases of pulmonary hypertension have been reported. Lymphocytosis (likely representing T/NK cells) that persisted for >12 months occurred in one-third of patients treated with dasatinib and these patients were more likely to have pleural effusions and favorable cytogenetic and molecular responses [57]. Monitoring, dose adjustment, and other management for common early toxicities, cytopenias, prolongation of QTc interval, other cardiovascular events, bleeding/bruising, and pleural effusion are discussed below. (See 'Monitoring toxicity' below and 'Managing toxicity' below.)

- **Outcomes** – Dasatinib achieved 97 percent OS and 93 percent PFS at three years, and MMR in more than three-quarters of patients with CP CML [58]. The following trials directly compared dasatinib with imatinib:

- The DASISION trial randomly assigned 519 patients with previously untreated CML to dasatinib 100 mg daily versus imatinib 400 mg daily [14,59-61]. At five-year follow-up, compared with imatinib, dasatinib did not achieve superior PFS or OS, but 26 percent of patients initially treated with imatinib were subsequently treated with a 2G TKI. Dasatinib generally produced faster and deeper molecular responses, with MR at three months (84 versus 64 percent) and MMR 4.5 (42 versus 33 percent). After five years, progression to AP/BC occurred in 4.6 and 7.3 percent of patients treated with dasatinib and imatinib, respectively [14]. AEs led to discontinuation of therapy in 16 and 7 percent of patients treated with dasatinib and imatinib, respectively [14]. Except for pleural effusion (28 versus 1 percent), nonhematologic AEs (eg, nausea, vomiting, rash, myalgia) and hematologic AEs were less common with dasatinib than with imatinib.
- Similar results were noted in a randomized phase 2 study of dasatinib (100 mg daily) versus imatinib (400 mg daily) in 246 patients with newly diagnosed CP CML [58]. After three years, dasatinib and imatinib achieved similar estimated rates of OS (97 percent each), PFS (93 versus 90 percent, respectively), and relapse-free survival (91 versus 88 percent), but dasatinib resulted in higher rates of CCyR (84 versus 69 percent) and MMR at 12 months (59 versus 44 percent). Pleural effusions, headache, and diarrhea were more common with dasatinib, while edema, nausea, and muscle pain were more common with imatinib.

A lower starting dose of dasatinib may be effective, but we await long-term outcomes before suggesting its use outside of a clinical trial. In a phase 2 study, 81 patients with newly diagnosed CP CML were treated with dasatinib 50 mg daily; with >12 month follow-up, CCyR was achieved by 77 and 95 percent by 6 and 12 months, respectively [62]. At 12 months, cumulative MMR rate was 81 percent and MR4.0 and MR4.5 rates were 55 and 49 percent, respectively. The 50 mg daily dose was well tolerated, with pleural effusion in 6 percent.

Bosutinib — Bosutinib is a 2G TKI that is associated with cytopenias, diarrhea, abnormal liver function, and fluid retention. We generally avoid use of bosutinib in patients with liver or kidney dysfunction, diarrhea, and heart failure and caution is advised when it is given with certain medications.

- **Initial treatment** – For initial therapy of CP CML, the FDA-approved dose is 400 mg once daily [63]; this dose is better tolerated than 500 mg daily used in some studies (described below). Some clinicians begin with bosutinib 100 mg once daily and escalate the dose by 100 mg every week until reaching 400 mg daily, to reduce diarrhea or liver toxicity [64]. The daily dose should be reduced for patients with liver or kidney disease or those taking CYP3A4 inducers or inhibitors (table 6) and PPIs.
- **Toxicity** – Most AEs (table 4) are mild and self-limited. However, diarrhea, nausea, and abdominal pain occur commonly, and grade ≥3 diarrhea or abnormal liver function tests are each reported in approximately 8 percent, with most such toxicities occurring during the first one to two months of treatment and resolving thereafter [63].

Bosutinib should be temporarily held or the dose adjusted for significant gastrointestinal toxicity [63]. Monitoring, dose adjustment, and other management for common early toxicities, cytopenias, and gastrointestinal AEs are discussed below. (See 'Monitoring toxicity' below and 'Managing toxicity' below.)

- **Outcomes** – Bosutinib can achieve rates of cytogenetic and molecular responses that are comparable to other 2G TKIs and imatinib [16]. The following randomized trials directly compared bosutinib versus imatinib in newly diagnosed CP CML:

- The BELA trial randomly assigned 502 patients to bosutinib (500 mg daily) versus imatinib (400 mg daily) [65,66]. Bosutinib achieved faster cytogenetic responses but, compared with imatinib, similar rates of CCyR and MMR after ≥24 month follow-up. Bosutinib was associated with a lower rate of a composite outcome of disease progression/lack of efficacy (3 versus 10 percent, respectively), and responses to bosutinib did not differ based on Sokal score. Bosutinib was associated with more diarrhea and elevations of liver function tests and a higher rate of drug discontinuation due to adverse events (19 versus 6 percent) [65].
- The BFORE trial randomly assigned 536 adults to bosutinib (400 mg once daily) versus imatinib (400 mg once daily) [15]. Bosutinib achieved higher rates of MMR (47 versus 37 percent, respectively) and CCyR (77 versus 66 percent) at 12 months and reached these milestones more quickly. Any type of grade ≥3 toxicity occurred in 56 percent of patients receiving bosutinib and 43 percent of patients receiving imatinib; treatment was discontinued by 22 percent of patients receiving bosutinib and 27 percent of patients receiving imatinib. Bosutinib was associated with more grade ≥3 diarrhea (8

versus 1 percent, respectively) and elevated serum transaminases, but cardiac and vascular toxicities were uncommon with both treatments.

Other TKIs — Other TKIs have been approved for treatment of CML in specific clinical settings or countries:

- **Radotinib** is a 2G TKI approved by the Korea Food and Drug Administration (KFDA) for initial treatment of CML or CML that is refractory to other TKIs. Compared with imatinib, radotinib achieved faster cytogenetic and molecular responses in the RERISE study, which randomly assigned 241 patients with previously untreated CML to radotinib (either 300 or 400 mg twice daily) versus imatinib (400 mg once daily) [67]. Compared with imatinib, radotinib achieved superior MMR and CCyR at 12 months, and early molecular response at three months. Responses were similar with both doses of radotinib.
- **Flumatinib** is a 2G TKI available in China. In one trial, 394 patients with CP CML were randomly assigned to flumatinib (600 mg once daily) versus imatinib (400 mg once daily) [68]. At 12 months, compared with patients receiving imatinib, more patients receiving flumatinib achieved MR4 (23 versus 12 percent) and no patients progressed to AP/BC (versus four patients taking imatinib). This trial differed from other large phase 3 studies of 2G TKIs because only 7 percent of patients had high-risk CML.
- **Ponatinib** is a third-generation TKI that is approved for treatment of CML that is resistant or patients who are intolerant of prior TKIs, as discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Ponatinib'.)

TREATMENT RESPONSE

Response monitoring — Response to treatment with a tyrosine kinase inhibitor (TKI) is evaluated by the timely achievement of hematologic, cytogenetic, and molecular milestones (table 7). (See 'Definitions of response' below.)

- **Achievement of milestones** – For patients who achieve treatment milestones on schedule, sustain the response, and have acceptable levels of toxicity, treatment should continue indefinitely.

For certain patients, a trial of TKI discontinuation or de-escalation may be considered. (See 'TKI discontinuation for TFR' below.)

- **Failure to achieve milestones** – All patients who fail to achieve treatment response milestones (table 7) should be evaluated for adherence to treatment and possible drug interactions. Evidence of loss of response should be confirmed with repeat studies before treatment changes are initiated.

Management of CML that is resistant to TKI therapy is discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)

Serial measurement in peripheral blood of *BCR::ABL1* by quantitative polymerase chain reaction (qPCR) is the preferred method for monitoring treatment response; the qPCR assay should be standardized and have a sensitivity of ≥ 4.5 -log reduction from the baseline, as described below. (See 'Definitions of response' below.)

Optimal responses are:

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

After *BCR::ABL1* is ≤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 MMR (ie, MR3), this should be confirmed by repeating qPCR in one to three months.

Measurement of molecular response by qPCR has greater sensitivity than cytogenetic assays, and qPCR is the only tool that can monitor responses after a patient has achieved a complete cytogenetic response (CCyR).

It is not necessary to serially assess bone marrow for cytogenetic or molecular response. We generally reserve additional bone marrow biopsies for patients exhibiting resistance to a TKI, progression of CML, development of dysplasia or cytopenias. However, for patients who have additional cytogenetic abnormalities that are detected in Philadelphia chromosome (Ph)-negative cells, it may be necessary to monitor progression of that clone with serial cytogenetic studies, as described below. (See 'Additional chromosomal abnormalities' below.)

Our approach to monitoring disease in patients in chronic phase is consistent with those proposed by the European LeukemiaNet (table 1 and algorithm 2) [69] and National Cancer Center Network (NCCN) [70].

Definitions of response

Clinical and cytogenetic responses

- **Hematologic response** – Hematologic response is assessed by the white blood cell (WBC) count, differential, platelet count, and improvement in splenomegaly [69,71]:
 - **Complete hematologic response (CHR)** is defined by normalization of all peripheral blood counts, WBC count <10,000/microL, platelet count <450,000/microL, no circulating immature myeloid cells (eg, blasts, promyelocytes, myelocytes), and no clinical findings of disease, including disappearance of a palpable spleen [72].
- **Cytogenetic response** – Cytogenetic response is assessed by chromosome banding of ≥20 bone marrow cell metaphases:
 - **Complete cytogenetic response (CCyR)**: No Ph+ metaphases detected
 - **Major cytogenetic response**: 0 to 35 percent Ph+ metaphases
 - **Minor cytogenetic response**: >35 percent Ph+ metaphases

We consider that fluorescence *in situ* hybridization (FISH) is not a preferred method for monitoring cytogenetic response, because it will not detect the emergence of additional chromosomal abnormalities, and the risk of false positive or false negative findings given the limited number of cells that are typically analyzed by interphase FISH [73]. Although FISH <1 percent generally corresponds to CCyR, endpoints for cytogenetic response with FISH have not been defined [74,75].

Molecular response

- **Molecular response** – Molecular response is assessed by qPCR of *BCR::ABL1*, which compares the level of *BCR::ABL1* transcripts to other control genes (eg, *BCR*, *ABL1*, or *GUSB*) [24,76]. The results should be expressed using the IS, which assumes a standardized baseline value of 100 percent for all patients, and should have a sensitivity of $\geq 4.5\text{-log}$. Molecular response can be described as:
 - **Early molecular response (EMR)**: $BCR::ABL1 \leq 10$ percent at three and/or six months.
 - **Major molecular response (MMR)**: $BCR::ABL1 \leq 0.1$ percent.
 - **Undetectable *BCR::ABL1***: The level of sensitivity of the assay should be provided in the report (eg, MR4, MR4.5). To illustrate this concept, a value of MR4 corresponds to detection of one CML cell among 10,000 (ie, 10^4) normal cells.

Molecular response can also be described by the log reduction below the standard 100 percent baseline value of the IS:

- **MR2** – $BCR::ABL1 \leq 1$ percent (ie, ≥ 2 log reduction from the standardized baseline); this level roughly corresponds to CCyR.
- **MR3** – $BCR::ABL1 \leq 0.1$ percent (ie, ≥ 3 log reduction); MR3 is equivalent to MMR.
- **MR4** – $BCR::ABL1 \leq 0.01$ percent (ie, ≥ 4 log reduction).
- **MR4.5** – $BCR::ABL1 \leq 0.0032$ percent (ie, ≥ 4.5 log reduction); this is the current limit of most commercially available assays.

MONITORING TOXICITY

Our approach for monitoring toxicity of all tyrosine kinase inhibitors (TKI) includes history, physical examination, laboratory studies, and specialized evaluations, as needed. For adverse events (AE) that are more common or severe with specific TKIs, additional monitoring is suggested above. (See 'Individual TKIs' above.)

- **History and physical examination** – History should include assessment of common early toxicities that may occur with all TKIs, including nausea, muscle cramps, rash, edema, fatigue, and diarrhea.

A complete list of medications should be reviewed for potential interactions with TKIs. For patients taking nilotinib or dasatinib it is particularly important to consider medications that may prolong the

QTc interval (table 5) and inhibitors or inducers of cytochrome P450 3A (table 6) and review of cardiovascular risk factors.

Review of systems should elicit a history of bleeding or bruising; chest pain, shortness of breath, palpitations, claudication, or other symptoms that may indicate cardiovascular complications; cough or dyspnea that may suggest pleural effusion, pulmonary hypertension, or interstitial lung disease; jaundice, abdominal pain, persistent nausea/vomiting, bleeding, or other findings that suggest liver disease, pancreatitis, or gastrointestinal bleeding.

Physical examination should focus on the following:

- **Imatinib** – Peripheral and periorbital edema and rash.
- **Nilotinib** – Jaundice, hepatomegaly, abdominal tenderness that may suggest liver disease or pancreatitis; pallor or reduced pulses of extremities, carotid bruit, cardiac dysrhythmia, edema that may suggest cardiovascular disease.
- **Dasatinib** – Chest auscultation and cardiac exam, bleeding/bruising; edema, cardiac dysrhythmia, fluid retention, tachypnea, or other findings consistent with cardiovascular disease or pleural effusion.
- **Bosutinib** – Abdominal pain, jaundice, or other findings associated with liver disease.
- **Complete blood count** (CBC) with differential count every two weeks for the first two months of TKI therapy, monthly for the next six months, and then as needed.
- **Serum chemistries** should include renal, liver function tests, and uric acid every two weeks for the first two months, then as clinically indicated. In addition, we suggest the following:
 - Potassium, phosphate, and magnesium for patients taking nilotinib and dasatinib.
 - Lipase and amylase in the first several months of treatment for patients taking nilotinib, dasatinib, and bosutinib.
- **Other testing** – We do not suggest routine imaging or other studies, unless it is suggested for the specific TKI. Examples include:
 - Electrocardiograms (EKG) to evaluate the QTc interval for patients taking nilotinib or dasatinib.
 - Chest radiograph for patients with a cough or dyspnea who are taking dasatinib.

MANAGING TOXICITY

Management of toxicity is crucial for long-term adherence to a tyrosine kinase inhibitor (TKI) regimen. Most patients with CML will require TKI therapy for the remainder of life, so maintaining treatment adherence requires effective management of both short-term and long-term toxicity. Persistent low-grade toxicities can adversely affect quality of life (QoL) and are barriers to long-term treatment adherence. Clinicians may

underestimate the impact of grade 1 to 2 adverse events (AE), so the importance of reporting AEs should be emphasized at the initiation of TKI therapy and repeatedly during treatment.

Key principles — In the first months of therapy, all TKIs are associated with certain common early toxicities (eg, rash, nausea, fatigue, edema, fatigue, myalgias/arthritis). However, each TKI also has certain distinctive short-term or long-term toxicities (table 4). (See 'Choosing a TKI' above and 'Individual TKIs' above.)

TKI-associated AEs typically:

- Arise in the first year of treatment, although some (eg, cardiovascular AEs with dasatinib or nilotinib) may not emerge for many months or years.
- Are mostly mild to moderate in intensity (ie, grade ≤2).
- Resolve spontaneously or can be controlled by dose adjustments.

We attempt to ameliorate AEs with symptomatic management, avoidance of medications that may exacerbate the toxicity, and judicious TKI dose adjustment or brief interruption. However, dose reductions should be undertaken with careful monitoring of molecular response to avoid administering a subtherapeutic dose. Extended interruptions of TKI treatment should be avoided because they may affect disease outcomes.

Once a deep molecular response is achieved, it may be possible to reduce the dose or temporarily discontinue the TKI to ameliorate low-grade AEs and/or lessen long-term complications, while still maintaining the remission. In a multicenter study, remission was sustained after 12 months of half-dose TKI therapy (ie, imatinib 200 mg daily, dasatinib 50 mg daily, or nilotinib 200 mg twice daily) in 162 of 174 patients (93 percent) patients who had taken a TKI for ≥3 years and achieved at least major molecular response (MMR; ie, <0.1 percent *BCR::ABL1* ratio) for ≥12 months [77]. The rate of recurrence was unrelated to the specific TKI or duration of TKI therapy, but was lower in patients who entered the study with MR4 (2 percent recurrence) than in those with MR3 (19 percent); remission was regained within four months of full dose therapy in all patients. Importantly, AEs (eg, lethargy, diarrhea, rash, nausea) improved during the three months of de-escalation, but not thereafter.

For severe, intractable TKI-associated toxicity, a change to an alternative TKI is discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)

TKI-associated AEs affect treatment adherence [78] and poor adherence to treatment may worsen clinical outcomes. A study that electronically monitored imatinib adherence in 87 patients with stable complete cytogenetic response reported that treatment adherence was an independent predictor of MMR; patients with ≥90 percent adherence had a significantly higher rate of MMR at six years (95 versus 28 percent), whereas no patient who took ≤80 percent of the prescribed dose attained a MMR [79].

TKI-associated AEs impair the QoL in patients with CML. A survey-based study of 448 patients with CML treated with imatinib for a median of five years reported that patients >60 years old had health-related QoL (HRQoL) scores similar to an age-matched general population, but younger patients reported significantly

worse HRQoL than controls [80]. Other studies reported that one-third to one-half of patients taking TKIs experienced symptoms that affected mood, general well-being, enjoyment of life, or interfered with daily functioning [81,82]. Randomized trials have reported no difference in QoL between patients taking imatinib and either nilotinib or dasatinib [83,84]. (See 'Nilotinib' above and 'Dasatinib' above.)

Common early toxicities — Certain AEs, including nausea, muscle cramps, rash, and edema, can occur with all TKIs in the first months of therapy, although some are more common or severe with particular TKIs (table 4). Most early toxicities can be managed with symptomatic care, avoidance of medications that may exacerbate the toxicity, and temporarily reducing or holding the TKI.

Common early AEs include:

- **Nausea** – Mild nausea is common early in the course of treatment with all TKIs, but it is generally most severe or persistent with imatinib and bosutinib; the incidence of nausea is decreased when these TKIs are taken with food. It is important to emphasize that nilotinib should **not** be taken with food. If the patient experiences persistent, severe TKI-associated nausea and/or vomiting, a trial of antiemetics may be beneficial. (See "Approach to the adult with nausea and vomiting", section on 'Treatment'.)
- **Muscle cramps** – All TKIs can cause muscle cramps, which most often affect the calves, feet, and hands. Mild cramps are most common with imatinib (approximately half of patients), but can be more severe (grade ≥3) in approximately 2 percent of patients [19]. There is no universally effective treatment for cramps, but electrolyte abnormalities should be corrected. Anecdotally, some patients benefit from calcium or magnesium supplements. Other symptomatic management is described separately. (See "Nocturnal leg cramps", section on 'Management').
- **Rash** – A mild, maculopapular rash occurs in up to one-half of patients treated with TKIs, which generally resolves with continued treatment [85-88]. Management of more persistent or troublesome rash is described separately. (See "Exanthematous (maculopapular) drug eruption", section on 'Management').
- **Edema** – Fluid retention can typically be managed by symptomatic care (eg, leg elevation, judicious use of diuretics). Periorbital edema is common with imatinib and does not respond to diuretic therapy. Liver, kidney, and/or cardiac function should be evaluated for more severe fluid retention, pleuro-pericardial effusion, or ascites. (See "Heart failure: Clinical manifestations and diagnosis in adults", section on 'Initial testing').
- **Diarrhea** – Diarrhea is most common with imatinib and bosutinib but generally resolves within weeks. Treatment with antidiarrheal agents (eg, loperamide) or temporary dose reductions maybe necessary to control diarrhea in some patients. It is important to question patients about possible lactose intolerance, which can exacerbate TKI induced diarrhea.
- **Fatigue** – Fatigue is a common symptom associated with TKI therapy. There are no specific remedies to TKI-associated fatigue. Careful dose reductions when patients achieve a deep molecular response may be useful for lessening symptomatic fatigue. Other causes of fatigue (eg, hypothyroidism, sleep disturbance) should be considered as contributing factors.

Hematologic

- **Cytopenias** – Mild to moderate cytopenias are common early in the course of treatment with all TKIs [89].

Early, mild TKI-associated cytopenias may be an anticipated, "on-target" effect that reflects the mechanism of action, rather than an allergic or adverse effect of TKIs [34]. At the time of diagnosis, circulating blood cells are dominated by progeny of the Ph+ clone, which are effectively eliminated by the TKI. Early cytopenias appear to reflect the slow recovery of normal, Ph-negative hematopoiesis; as a consequence, discontinuing or reducing the dose of the TKI may not solve the problem.

- For most patients, the TKI can be continued with the expectation of improvement in blood counts over time as normal hematopoiesis recovers.
- In a minority of patients, severe or symptomatic cytopenias (eg, infection, bleeding) may require a dose reduction or temporary discontinuation of the TKI. This is usually followed by a gradual improvement in counts that permits restoration of the TKI dose but, occasionally, longer-term treatment with a lower dose of the TKI is needed to maintain adequate blood counts.
- Rarely, critical cytopenias develop:
 - Neutropenia or thrombocytopenia – For persistent, severe neutropenia or thrombocytopenia, treatment with growth factors to stimulate recovery of normal hematopoiesis is safe and usually effective. Myeloid growth factors can ameliorate severe neutropenia, but there is less experience with platelet stimulating agents for severe thrombocytopenia. If hematopoietic growth factors are used to support normal hematopoiesis, an effort should be made to continue the TKI to prevent regrowth of the CML clone. (See "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation", section on 'Granulocyte colony stimulating factors' and "Clinical applications of thrombopoietic growth factors".)
 - Anemia – For patients with persistent symptomatic anemia, we check the reticulocyte count, ferritin, iron saturation, vitamin B12, and folate and correct any nutritional deficiencies detected. Transfusion support may be used if symptomatic. (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult".)

We suggest **not** treating TKI-associated anemia in CML with erythropoiesis-stimulating agents (ESA), because such treatment was associated with a higher rate of thrombosis in patients with CP CML and did not improve rates of survival or cytogenetic response [90]. The US Centers for Medicare and Medicaid Services (CMS) and the US Food and Drug Administration do not support the use of ESAs in patients with CML. (See "Role of erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer".)

- Should critical cytopenias persist, a switch to a different TKI can be considered because, for reasons that are not understood, count suppression can sometimes be less severe using an alternative TKI.

Management with an alternative TKI is discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)

- **Other hematologic toxicities** – Other TKI-associated toxicities include:

- **Bleeding** – Bleeding is generally caused by thrombocytopenia and should be managed as described above.

Gastrointestinal or other bleeding occurs in up to one-quarter of patients receiving dasatinib; it is less common with other TKIs [91-94]. Bleeding or bruising may be exacerbated by a qualitative platelet defect associated with dasatinib; such patients often have normal platelet counts and normal coagulation studies, but impaired platelet aggregation with arachidonic acid and/or epinephrine [95]. The bleeding is typically mild to moderate and usually responds to a drug holiday. Dasatinib should be used with caution in patients who require anticoagulants or medications that inhibit platelet function [56].

- **Follicular lymphoid hyperplasia** – Reversible follicular lymphoid hyperplasia has been reported as an uncommon event in patients taking a TKI, but the incidence is not well defined. A case series reported nine patients who developed progressive cervical lymph node enlargement while taking dasatinib [96]. Lymph node biopsy demonstrated follicular lymphoid hyperplasia without evidence of extramedullary blastic transformation of CML. Discontinuation of dasatinib resulted in a complete disappearance of nodal enlargement in all patients by two months.

For patients who develop follicular lymphoid hyperplasia, we suggest holding the TKI and observing the patient for clinical improvement. A decision to again administer the same TKI after resolution should be made on a case-by-case basis.

Other toxicity

- **Cardiovascular** – There is a substantial risk of cardiovascular (CV) and arterial thrombotic (AT) AEs in patients taking nilotinib. There is a slight increase of CV risk with dasatinib, and considerably less risk with the other TKIs used for initial treatment of CP CML. Older patients and those with pre-existing CV risk factors (eg, hypertension, diabetes, hyperlipidemia, smoking) are at greatest risk, irrespective of the TKI that is used, and the incidence ratio is highest in the early years of TKI therapy [97-99]. CV risks with individual TKIs are discussed above. (See 'Individual TKIs' above.)

Because most patients with CML are long-term survivors, it is important to perform a thorough baseline evaluation for CV risk factors and regular assessment and management of CV risk factors, including hypertension, lipids, and advice about smoking cessation. (See 'Pretreatment evaluation' above and 'Monitoring toxicity' above.)

Suggestions for management of specific CV and AT AEs include:

- **QTc prolongation and dysrhythmias** – Although uncommon, cardiac dysrhythmias (including prolonged QTc interval, palpitations) may occur with TKIs, and are most often seen with dasatinib and nilotinib. All patients who receive nilotinib or dasatinib should have a baseline

electrocardiogram (EKG) to measure pretreatment QTc interval, correction of electrolyte abnormalities, avoidance of other medications that may prolong QTc interval (table 5), and dose adjustment as needed. EKG should be performed seven days after initiation of nilotinib or dasatinib, following dose adjustments, and periodically during treatment. (See 'Nilotinib' above and 'Dasatinib' above.)

- **Arterial thrombotic events** – AT events (eg, coronary artery disease, cerebrovascular accident, peripheral artery disease) are most commonly seen with nilotinib, and less often with dasatinib. We suggest permanent discontinuation of nilotinib or dasatinib for symptomatic or progressive vascular disease. Acceptable alternatives include switching to imatinib or bosutinib or a trial of TKI discontinuation (for appropriate patients). Although a benefit is not proven, many clinicians offer low-dose aspirin for general CV prophylaxis in patients taking nilotinib or dasatinib. (See 'TKI discontinuation for TFR' below.)
- **Hypertension** – The incidence of hypertension is increased with all TKIs, but is most common with imatinib. Management should follow general principles. (See "Overview of hypertension in adults", section on 'Treatment'.)

CV/AT risk with the third-generation TKI, ponatinib, is discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Ponatinib').

- **Pulmonary** – Pulmonary complications most often arise early in the course of treatment with dasatinib, but they can occur later and with any TKI. Patients who develop dyspnea, dry cough, or other symptoms suggestive of pleural effusion or another pulmonary process should be evaluated by chest radiograph and other testing, as clinically warranted.
 - **Pleural effusion** – In some studies, up to one-third of patients treated with dasatinib developed pleural effusions (most often exudative) [56]. Other causes of pleural effusion (eg, disease progression, heart failure, renal dysfunction, infection) should be investigated. Some patients have required thoracentesis, insertion of a chest tube, pleurodesis, and/or interruption or reduction of TKI dose. In a study that compared various dasatinib doses, treatment with 100 mg once daily was associated with a lower incidence of pleural effusion without affecting short- or long-term efficacy [100]. Dasatinib-associated pleural effusion is discussed in more detail separately. (See "Pulmonary toxicity associated with antineoplastic therapy: Molecularly targeted agents", section on 'Dasatinib').
 - **Pulmonary arterial hypertension** – Rare cases of pulmonary arterial hypertension (PAH) have been reported among patients taking dasatinib [101,102]. Dasatinib should be permanently discontinued in patients diagnosed with PAH. (See "Pulmonary toxicity associated with antineoplastic therapy: Molecularly targeted agents", section on 'Dasatinib' and "Treatment and prognosis of pulmonary arterial hypertension in adults (group 1)".)
 - **Interstitial lung disease** – Interstitial lung disease has also been reported in patients receiving dasatinib. (See "Pulmonary toxicity associated with antineoplastic therapy: Molecularly targeted agents", section on 'Dasatinib').

Further description of pulmonary complications of TKIs is provided separately. (See "Pulmonary toxicity associated with antineoplastic therapy: Molecularly targeted agents", section on 'Bcr-Abl tyrosine kinase inhibitors'.)

- **Gastrointestinal** – Nausea, vomiting, and diarrhea are common early in the course of treatment with all TKIs, but especially with imatinib and bosutinib, as described above. (See 'Common early toxicities' above.)

- **Liver function** – Abnormal liver function tests can occur with all TKIs but are most common with bosutinib and nilotinib. Alcohol and medications that may cause liver damage should be avoided, and dose adjustments should be made, as described for each TKI in the United States prescribing information. Additional details are provided separately. (See "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Molecularly targeted agents", section on 'Specific agents'.)
- **Pancreatitis** – Lipase and amylase should be obtained monthly (or as clinically indicated) for the first months in patients taking nilotinib. (See 'Monitoring toxicity' above.)

For clinically significant symptoms or abnormal lipase/amylase, the TKI dose should be reduced or suspended until improvement; if symptoms or laboratory abnormalities do not improve, the patient should be treated with an alternative TKI. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)

- **Gastrointestinal bleeding** – Management of gastrointestinal bleeding due to thrombocytopenia or a qualitative platelet disorder is described above. (See 'Hematologic' above.)

- **Other toxicities**

- **Hypophosphatemia** – Hypophosphatemia has been reported in patients taking nilotinib or larger doses of imatinib [20,103,104]. It is unknown whether hypophosphatemia results in long-term metabolic changes in bone. One report noted increased trabecular bone volume in patients receiving long-term imatinib, which may be due to promotion of osteoblast maturation and/or inhibition of osteoclast maturation and function via inhibition of platelet-derived growth factor [105].
- **Gynecomastia** – In one series, gynecomastia was noted in 7 of 38 men receiving imatinib and was associated with reduced levels of free testosterone [106].
- **Cancer** – TKIs do not appear to be associated with an increased risk of second malignancy. Analysis of 1445 patients treated with a TKI for CML or other hematologic malignancy and followed for a median of 107 months reported rates of second cancers comparable to those in the Surveillance, Epidemiology, and End Results (SEER) database [107].

TKI DISCONTINUATION FOR TFR

Patients may seek a treatment-free remission (TFR) because of tyrosine kinase inhibitor (TKI) toxicity, convenience, cost of medication, a desire to become pregnant, or for other reasons.

Approximately one-half of patients who meet the criteria for a trial of TKI discontinuation (described below) remain in a long-term TFR. Consequently, a sustained TFR can be anticipated in approximately 10 to 15 percent of patients with newly diagnosed CML (ie, one-half of the approximately one-third of patients who achieve a sustained, deep molecular remission).

- **Criteria for a trial of TKI discontinuation** – Outside of a clinical trial, **all** of the following criteria should be met:

- Age ≥ 18 years old
- Reliably taking TKI for ≥ 3 years
- No prior resistance to a second-generation (2G) TKI that required switching to another agent
- Prior evidence of a quantifiable *BCR::ABL1* transcript
- Stable molecular response (ie, MR4; *BCR::ABL1* ≤ 0.01 percent by the International Scale [IS]) (table 1) for ≥ 2 years, as documented by ≥ 4 separate tests performed ≥ 3 months apart
- Access to a reliable quantitative polymerase chain reaction (qPCR) test that is capable of detecting at least MR4.5 and can provide results within two weeks

- **Adverse effects of TKI discontinuation** – Aggravation or new development of musculoskeletal pain has been reported in 25 to 42 percent of patients who discontinued a TKI [108,109].

- **Monitoring**

- **First six months** – Monthly measurement of *BCR::ABL1* by qPCR
- **Next 18 months** – Every two months

Subsequent monitoring is described below.

- **Response to results**

- Loss of MR3 – For patients with loss of MR3 after TKI discontinuation, we suggest repeat testing within two weeks. If repeat testing confirms loss of MR3, the TKI should be resumed within four weeks.

Monitoring by qPCR should continue every four weeks until MR4 is re-established, then every 12 weeks indefinitely. For the rare patient who fails to again achieve MR4 three months after TKI is re-initiated, *BCR::ABL1* kinase domain mutation testing should be performed. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Initial management'.)

- Sustained MR3 – For patients with sustained MR3, *BCR::ABL1* should be measured by qPCR every three months. After several years of sustained MR3, we generally lengthen the monitoring interval

to four to six months, but we continue testing indefinitely because late relapses (eg, >2 years) have been reported [110].

Approximately half of patients remain in a TFR after discontinuing a TKI, according to multiple prospective discontinuation trials. In general, patients who are most likely to maintain a long TFR are those who have had the longest period of prior TKI treatment and/or had undetectable transcript levels for many years [111,112]. However, even among individuals who have achieved sustained MR4.5, about half will have evidence of molecular recurrence within one year after discontinuing TKI therapy, since viable CML stem cells can remain in a quiescent state in the marrow [113-120]. Nevertheless, almost all patients who show evidence of progression can again achieve a deep molecular response upon resumption of therapy.

Following are examples of studies that evaluated TKI discontinuation:

- EURO-SKI (European Stop Kinase Inhibitor) is a multicenter, prospective trial of TKI discontinuation that enrolled 758 patients in 11 countries, of whom 94 percent were taking imatinib [121]. In patients who had sustained MR3 for ≥1 year and taken a TKI for ≥3 years, molecular relapse-free survival was 50 percent (95% CI 46-54 percent) at 24 months.
- LAST (Life After Stopping TKIs) is a prospective multicenter study of 173 patients in the United States who were taking imatinib (60 percent of patients), dasatinib, nilotinib, or bosutinib and had achieved MR4.0 for ≥2 years [122]. With a median follow-up of 42 months (4 to 62), 61 percent of patients remained in a TFR. In addition, 80, 35, 88, and 21 percent had a clinically meaningful improvement of fatigue, depression, diarrhea, and sleep disturbance, respectively. Restarting a TKI resulted in worsening of patient reported outcomes.

Similar results have been reported by discontinuation trials in patients receiving nilotinib or dasatinib [108,123-135].

SPECIAL SETTINGS

Additional chromosomal abnormalities — Detection of additional cytogenetic abnormalities (ACAs; ie, cytogenetic abnormalities in addition to t(9;22)) at the time of diagnosis may affect response to initial treatment and influence the protocol for response monitoring. The impact of ACAs may vary with the nature of the abnormality and whether it is detected in the same cells that carry the Philadelphia chromosome (Ph) versus a separate clonal population.

ACAs are reported in 5 to 10 percent of patients at the time of diagnosis of CP CML [136]. For patients treated with tyrosine kinase inhibitors (TKI), the prognostic significance of ACAs detected at the time of diagnosis of CP CML is uncertain. This variability may reflect differences associated with specific cytogenetic abnormalities [137-141]. It has been proposed that the more common abnormalities ("major route abnormalities") can be classified as good prognosis (eg, trisomy 8, -Y, extra copy of Ph) or poor prognosis (eg, i(17)(q10), -7/del7q, 3q26.2) [142]. ACAs are known to be associated with adverse outcomes for patients with CP CML who were previously treated with interferon (IFN) alfa and other agents, and for patients with CML in accelerated phase or blast crisis [137].

Monitoring of the response to therapy is influenced by whether the ACA is present in the same cell as t(9;22)/BCR/ABL1 (ie, Ph+) or in Ph-negative (Ph-) cells; metaphase cells from the initial marrow aspirate are needed to make this distinction (see 'Pretreatment evaluation' above):

- **ACA in Ph+ cells** – If the ACA is present in the same cell as t(9;22)/BCR/ABL1, cases can be monitored with quantitative polymerase chain reaction (qPCR) on the blood (as described above), because the ACA will disappear as the Ph+ cells disappear. (See 'Response monitoring' above.)
- **ACA in Ph- cells** – If the ACA is present in Ph- cells, monitoring of the ACA clone will require serial bone marrow evaluations or monitoring of peripheral blood with a fluorescence in situ hybridization (FISH) probe that can detect the specific abnormality. In addition, response of CML to initial therapy must be monitored by qPCR.

Pregnancy — TKIs are contraindicated in women who seek to become pregnant and in the first trimester of pregnancy because of increased rates of miscarriage and fetal abnormalities [143,144]. Safety of TKIs in the second and third trimesters is not well defined. TKIs are not known to affect fertility in men or increase the rate of miscarriage or fetal abnormalities in female partners of men taking a TKI [145-149].

Conception while on a TKI and treatment with a TKI during the first trimester is strongly discouraged because of the risk of fetal abnormalities; otherwise, there is no consensus regarding optimal monitoring and management of CML during pregnancy [150,151]. We suggest monthly monitoring *BCR::ABL1* by qPCR and initiation of treatment if *BCR::ABL1* increases to ≥1.0 percent. (See 'Definitions of response' above.)

Our approach follows:

- **First trimester** – For women who require treatment in the first trimester, we suggest leukapheresis and/or IFN alfa rather than TKI therapy, because of their more favorable balance of benefit versus toxicity. IFN alfa is safe during pregnancy; some experts consider hydroxyurea safe in this setting [150,152-157]. Low dose aspirin and/or low molecular weight heparin may be used for thrombocytosis [158,159].
- **Later pregnancy** – In the second or third trimester, the potential benefit of a TKI to the mother must be weighed against risks to the fetus; IFN alfa, leukapheresis, or other approaches may be preferable in this setting.
- **Nursing** – Women should not breast feed while taking a TKI because it can pass into human breast milk and may impair growth and/or development of the infant [160,161].
- **Men** – We do not discontinue TKIs for male patients attempting conception. Our approach is consistent with European LeukemiaNet 2020 guidelines and opinions of other experts [6,162,163].

More than one-third of patients were of reproductive age at the time that CML was first diagnosed, according to a population-based registry study [164]. A study of 180 women exposed to imatinib during pregnancy reported that half of pregnancies with known outcomes were normal, but 10 percent had fetal abnormalities that ended in spontaneous abortion [143]. Among 46 women who received dasatinib during pregnancy, one-

third delivered a normal infant, but elective or spontaneous abortion occurred in 39 and 17 percent, respectively, 11 percent had an abnormal pregnancy, and there were fetal abnormalities in 15 percent [144].

Among men, some clinical studies have suggested reduced spermatogenesis with TKIs, but there are multiple reports of successful pregnancy and no increased risk for congenital abnormalities among offspring from partners of male patients receiving TKIs [132,144,165-170]. As an example, among 17 men treated with bosutinib, the outcome of 14 pregnancies was known; nine patients had full term healthy babies, four had an induced abortion, and one had a spontaneous abortion [165]. Among men treated with dasatinib, 91 percent of 30 female partners delivered infants who were normal at birth [144].

Children — CML is rare in children, and it accounts for <3 percent of all pediatric leukemias [171-173]. There are no evidence-based guidelines for treatment of pediatric CML, and risk stratification tools have not been validated in children. We urge participation in a clinical trial, whenever possible. Outside of a clinical trial, some experts follow guidelines designed for treatment of adult patients.

Imatinib and dasatinib are the only TKIs that are approved by the US Food and Drug Administration for treatment of children; safety and efficacy of other TKIs in children are poorly defined. We suggest **not** using the clinical scoring systems to stratify pediatric treatment of CML because these models have not been validated in children. A study that evaluated 90 children with CML reported high discordance between the Sokal, Euro, and EUTOS methods [174].

Children may require decades of treatment, and it is important to monitor children for long-term side effects of TKIs, such as delayed growth, altered bone metabolism, thyroid abnormalities, and effects on puberty and fertility [175]. Growth should be monitored closely, and an endocrinologist should be consulted for impaired longitudinal growth in children [176-180].

Studies of TKIs for treatment of pediatric CML include:

- **Imatinib** – A French study included 44 children (age: 10 months to 17 years) with CP CML who were treated with imatinib (260 mg/m^2) [181]. With median follow-up of 31 months, the rate of complete hematologic response (CHR) was 98 percent, and estimated progression-free survival (PFS) at 36 months was 98 percent. After 12 months, rates of complete cytogenetic response (CCyR) and major molecular response (MMR) were 61 and 31 percent, respectively. Early molecular response (ie, *BCR::ABL1* 10 percent [International Scale (IS)] at three months) correlated with better PFS and higher rates of CCyR and MMR at 12 months [182].

An Italian study of 47 children with CP CML reported that higher dose imatinib (340 mg/m^2) was effective and well tolerated [183,184]. CCyR was achieved in 92 percent at six months, and at 12 months MMR (≤ 0.01 percent *BCR::ABL1* IS) and MR4 were achieved in 67 and 33 percent of patients, respectively.

- **Dasatinib** – Dasatinib (60 mg/m^2 to 120 mg/m^2) was tolerated in a study of children with newly diagnosed, relapsed, or refractory CML [185].

There are no reports of TKI discontinuation in children.

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 AND RECOMMENDATIONS

- **Description** – Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that is associated with the Philadelphia chromosome t(9;22)(q34;q11) and the *BCR::ABL1* fusion gene, which produces a constitutively active *BCR::ABL1* tyrosine kinase. Chronic phase (CP) CML can progress from a relatively indolent disorder to accelerated phase (AP) or blast crisis (BC).
- **Goals of treatment** – The goals for management of CP CML are to achieve clinical remission, maintain long-term disease control, and avoid disease progression to AP or BC, while optimizing quality of life by limiting treatment-related toxicity. For patients who achieve a sustained and deep molecular remission, a trial of discontinuation of therapy to achieve a treatment-free remission (TFR) is a long-term goal of management. (See 'Goals of care' above.)
- **Pretreatment evaluation** – Pretreatment evaluation should include history, physical examination, specific laboratory studies, and determination of CML risk category (using either the Sokal, Euro, EUTOS, or ELTS tools) (table 3). (See 'Pretreatment evaluation' above and 'CML risk score' above.)
- **Treatment with a tyrosine kinase inhibitor (TKI)** – With the exception of CML diagnosed during pregnancy, we recommend a *BCR::ABL1* TKI for initial treatment of all patients with CP CML (**Grade 1A**),

based on superior treatment outcomes and modest toxicity compared with other treatments (eg, cytotoxic agents, interferons, hematopoietic cell transplantation). (See 'Rationale for TKI treatment' above.)

- **Choosing a TKI** – We stratify selection of a BCR::ABL1 TKI according to the CML risk score and the goal of achieving a TFR. No individual TKI is preferred for initial treatment of all patients with CP CML. The choice of a particular TKI must also consider the side effect profile (table 4), comorbid illnesses, availability, cost, and patient preference (see 'CML risk score' above and 'Choosing a TKI' above):

- **High-risk CML** – For patients with high-risk CP CML, we suggest treatment with a second-generation (2G) TKI (eg, nilotinib, dasatinib, bosutinib), when available, rather than imatinib (**Grade 2B**).

Progression to AP/BC is a concern in patients with high-risk CML and, compared with imatinib, 2G TKIs may be associated with lower rates of disease progression. However, imatinib and 2G TKIs produce comparable rates of overall survival (OS), progression-free survival (PFS), and adverse events (AE) in high-risk CML.

- **Low- or intermediate-risk CML** – For patients with low-risk or intermediate-risk CP CML, the choice of a TKI is influenced by the importance assigned to achievement of a TFR (algorithm 1):

- **TFR is an important goal** – For patients with low- or intermediate-risk CP CML who consider a TFR an important goal, we suggest a 2G TKI (eg, nilotinib, dasatinib, bosutinib) rather than imatinib (**Grade 2C**), because 2G TKIs are associated with faster and deeper responses and are more likely to enable a trial of TKI discontinuation. (See 'TFR is an important goal' above.)

Eligibility criteria for a trial of TKI discontinuation and outcomes are described above. (See 'TKI discontinuation for TFR' above.)

- **TFR is NOT an important goal** – For patients who do **not** consider achieving a TFR a high priority, treatment with imatinib or a 2G TKI (eg, nilotinib, dasatinib, bosutinib) is acceptable, because they achieve comparable rates of OS, PFS, and AEs.

- **Dose, toxicities, and outcomes** – Initial treatment dose, toxicities, and outcomes with individual TKIs are presented for the individual TKIs. (See 'Individual TKIs' above.)
- **Monitoring** – We monitor response to TKI therapy with serial measurement of *BCR::ABL1* by quantitative polymerase chain reaction (qPCR) in peripheral blood, cytogenetics, and hematologic parameters at regular intervals (algorithm 3), as described above. (See 'Response monitoring' above.)
- **Toxicity** – Management of TKI toxicity is crucial for maintaining treatment adherence and achieving optimal outcomes. Some toxicities are common to all TKIs (eg, cytopenias, rash, nausea, fatigue, muscle cramps), but each agent is also associated with certain "defining" toxicities. Examples of defining toxicities include:
 - Imatinib – Muscle cramps, fatigue, edema, nausea, diarrhea
 - Nilotinib – Cardiovascular (CV) toxicity (including coronary, cerebral, and peripheral vascular disease), prolonged QTc interval, hyperglycemia, pancreatitis

- Dasatinib – Pleural effusion, pulmonary hypertension, prolonged QTc interval, platelet dysfunction
- Bosutinib – Diarrhea, abnormal liver function, rash

Our approach to managing TKI toxicity is discussed above. (See 'Managing toxicity' above.)

- **Treatment-free remission** – For patients who achieve a long-standing, deep molecular response and are expected to comply with the demands of frequent testing and follow-up, a trial of TKI discontinuation is an acceptable option. Criteria for a TKI discontinuation trial and management are discussed above. (See 'TKI discontinuation for TFR' above.)
- **Pregnancy** – TKIs are contraindicated in women who seek to become pregnant, in early pregnancy, and in nursing mothers because of increased rates of miscarriage/fetal abnormalities and potential effects of growth and development in infants. There are no restrictions for men who wish to father a child while on TKI therapy. Management of CML in pregnancy and in children is discussed above. (See 'Pregnancy' above.)

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GRAPHICS

Recommendations for cytogenetic and molecular monitoring for patients with chronic myeloid leukemia

At diagnosis	Chromosome banding analysis (CBA) of marrow cell metaphases FISH in case of Ph negativity to identify variant, cryptic translocations Qualitative PCR (identification of transcript type)
During treatment	Quantitative real-time PCR (RQ-PCR) for the determination of <i>BCR-ABL1</i> transcripts level, to be performed every three months until an MMR (<i>BCR-ABL1</i> ≤ 0.1 percent, or MR $^{3.0}$) has been achieved, then every three to six months and/or CBA of marrow cell metaphases (at least 20 banded metaphases), to be performed at 3, 6, and 12 months until a CCyR has been achieved, then every 12 months. Once a CCyR is achieved, FISH on blood cells can be done. If adequate molecular monitoring can be ensured, cytogenetics can be spared.
Failure, progression	RQ-PCR, mutational analysis, and CBA of marrow cell metaphases. Immunophenotyping in BP.
Warning	Molecular and cytogenetic tests to be performed more frequently. CBA of marrow cell metaphases recommended in case of myelodysplasia or CCA/Ph- with chromosome 7 involvement.

The responses can be assessed either with molecular tests alone or with cytogenetic tests alone, depending on the local laboratory facilities; but, whenever possible, both cytogenetic and molecular tests are recommended until a CCyR and an MMR are achieved. Then RQ-PCR alone may be sufficient. Mutational analysis by conventional Sanger sequencing is recommended in case of progression, failure, and warning. In case of failure, warning, and development of myelodysplastic features (unexpected leucopenia, thrombocytopenia, or anemia), CBA of marrow cell metaphases is recommended.

FISH: fluorescence in situ hybridization; PCR: polymerase chain reaction; CBA: chromosome banding analysis; CCyR: complete cytogenetic response; CCA/Ph-: clonal chromosome abnormalities in Ph- cells.

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Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance status measures

Karnofsky		ECOG	
Score	Definition	Score	Definition
100	Normal, no complaints, no evidence of disease	0	Fully active; no performance restrictions
90	Able to carry on normal activity, minor signs or symptoms of disease	1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
80	Normal activity with effort, some signs or symptoms of disease	2	Capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
70	Cares for self, unable to carry on normal activity or to do active work	3	Capable of only limited self-care; confined to bed or chair >50% of waking hours
60	Requires occasional assistance but is able to care for most needs	4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair
50	Requires considerable assistance and frequent medical care	5	Dead
40	Disabled, requires special care and assistance		
30	Severely disabled, hospitalization is indicated, although death is not imminent		
20	Hospitalization is necessary, very sick, active supportive treatment necessary		
10	Moribund, fatal processes progressing rapidly		
0	Dead		

Graphic 57945 Version 11.0

Prognostic scoring systems for newly diagnosed chronic myeloid leukemia*

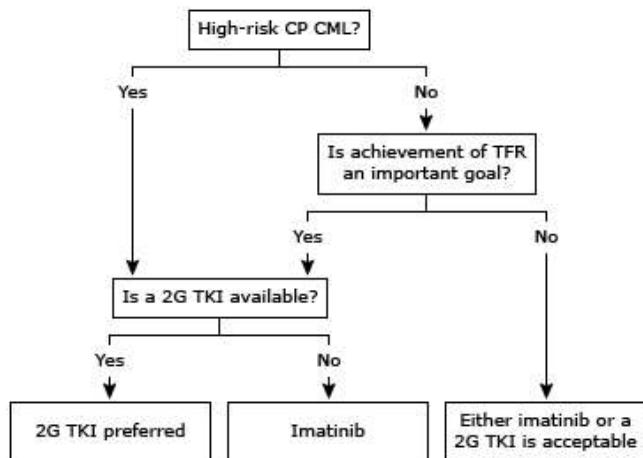
Scoring system	Calculator Link	Risk groups
EUTOS score ^[1]	www.leukemia-net.org/content/leukemias/cml/eutos_score/	Low risk, high risk
Euro (Hasford) score ^[2]	www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/	Low risk, intermediate risk, high risk
Sokal score ^[3]	www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/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

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Selection of a BCR-ABL1 TKI for initial treatment of chronic phase CML



Selection of a TKI must consider the toxicity profile, comorbid illnesses, availability, cost, and patient preference. Refer to related UpToDate topics for details of CML risk scoring, eligibility for TKI discontinuation to achieve TFR, outcomes, and adverse effects of individual BCR-ABL1 TKIs.

TKI: tyrosine kinase inhibitor; CP: chronic phase; CML: chronic myeloid leukemia; 2G: second generation; TFR: treatment-free remission.

Graphic 130520 Version 1.0

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-like effect; arterial thrombosis. Black box warning: cardiovascular events; hepatic toxicity.	Active against <i>BCR::ABL1 T315I</i> mutation; limited long-term safety data

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
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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.

Graphic 89930 Version 4.0

Some reported causes and potentiators of the long QT syndrome

Congenital																			
<ul style="list-style-type: none"> ▪ Jervell and Lange-Nielsen syndrome (including "channelopathies") ▪ Romano-Ward syndrome ▪ Idiopathic 																			
Acquired																			
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Metabolic disorders</th><th style="text-align: left;">Other factors</th><th style="text-align: left;">Androgen deprivation therapy</th><th style="text-align: left;">Diuretic therapy via electrolyte disorders particularly hypokalemia and hypomagnesemia</th></tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> ▪ Hypokalemia ▪ Hypomagnesemia ▪ Hypocalcemia ▪ Starvation ▪ Anorexia nervosa ▪ Liquid protein diets ▪ Hypothyroidism </td><td> <ul style="list-style-type: none"> ▪ Myocardial ischemia or infarction, especially with prominent T-wave inversions ▪ Intracranial disease ▪ HIV infection ▪ Hypothermia ▪ Toxic exposure: Organophosphate insecticides </td><td> <ul style="list-style-type: none"> ▪ GnRH agonist/antagonist therapy ▪ Bilateral surgical orchiectomy </td><td>Herbs</td></tr> <tr> <td> Bradyarrhythmias <ul style="list-style-type: none"> ▪ Sinus node dysfunction ▪ AV block: Second or third degree </td><td></td><td></td><td> <ul style="list-style-type: none"> ▪ Cinchona (contains quinine), iboga (ibogaine), licorice extract in overuse via electrolyte disturbances </td></tr> </tbody> </table>				Metabolic disorders	Other factors	Androgen deprivation therapy	Diuretic therapy via electrolyte disorders particularly hypokalemia and hypomagnesemia	<ul style="list-style-type: none"> ▪ Hypokalemia ▪ Hypomagnesemia ▪ Hypocalcemia ▪ Starvation ▪ Anorexia nervosa ▪ Liquid protein diets ▪ Hypothyroidism 	<ul style="list-style-type: none"> ▪ Myocardial ischemia or infarction, especially with prominent T-wave inversions ▪ Intracranial disease ▪ HIV infection ▪ Hypothermia ▪ Toxic exposure: Organophosphate insecticides 	<ul style="list-style-type: none"> ▪ GnRH agonist/antagonist therapy ▪ Bilateral surgical orchiectomy 	Herbs	Bradyarrhythmias <ul style="list-style-type: none"> ▪ Sinus node dysfunction ▪ AV block: Second or third degree 			<ul style="list-style-type: none"> ▪ Cinchona (contains quinine), iboga (ibogaine), licorice extract in overuse via electrolyte disturbances 				
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Bradyarrhythmias <ul style="list-style-type: none"> ▪ Sinus node dysfunction ▪ AV block: Second or third degree 			<ul style="list-style-type: none"> ▪ Cinchona (contains quinine), iboga (ibogaine), licorice extract in overuse via electrolyte disturbances 																
Medications*																			
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="4" style="text-align: left;">High risk</th></tr> </thead> <tbody> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Adagrasib ▪ Ajmaline[¶] ▪ Amiodarone[△] ▪ Arsenic trioxide ▪ Astemizole[◊] ▪ Bedaquiline ▪ Bepridil[◊] ▪ Chlorpromazine </td><td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Cisaparide (restricted availability) ▪ Delamanid[¶] ▪ Disopyramide[△] ▪ Dofetilide ▪ Dronedarone ▪ Haloperidol (IV) ▪ Ibutilide ▪ Ivosidenib </td><td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Lenvatinib ▪ Levoketoconazole ▪ Methadone ▪ Mobocertinib ▪ Papavirine (intracoronary) ▪ Procainamide ▪ Quinidine ▪ Quinine </td><td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Selpercatinib ▪ Sertindole[¶] ▪ Sotalol ▪ Terfenadine[◊] ▪ Vandetanib ▪ Vernakalant[¶] ▪ Ziprasidone </td></tr> <tr> <th colspan="4" style="text-align: left;">Moderate risk</th></tr> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Amisulpride[¶] (oral)[§] ▪ Azithromycin ▪ Capecitabine ▪ Carbetocin[¶] ▪ Certinib ▪ Chloroquine ▪ Citalopram ▪ Clarithromycin ▪ Clofazimine ▪ Clomipramine[¥] </td><td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Droperidol ▪ Encorafenib ▪ Entrectinib ▪ Erythromycin ▪ Escitalopram ▪ Etelcalcetide ▪ Fexinidazole ▪ Flecainide ▪ Flouxuridine ▪ Fluconazole </td><td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Inotuzumab ozogamicin ▪ Isoflurane ▪ Levetiracetam ▪ Levofloxacin (systemic) ▪ Lofexidine ▪ Meglumine antimoniate ▪ Midostaurin ▪ Moxifloxacin ▪ Nilotinib </td><td style="vertical-align: top;"> <ul style="list-style-type: none"> ▪ Propafenone ▪ Propofol ▪ Quetiapine ▪ Quizartinib ▪ Ribociclib ▪ Risperidone ▪ Saquinavir ▪ Sevoflurane ▪ Sparfloxacin[¶] ▪ Sunitinib </td></tr> </tbody> </table>				High risk				<ul style="list-style-type: none"> ▪ Adagrasib ▪ Ajmaline[¶] ▪ Amiodarone[△] ▪ Arsenic trioxide ▪ Astemizole[◊] ▪ Bedaquiline ▪ Bepridil[◊] ▪ Chlorpromazine 	<ul style="list-style-type: none"> ▪ Cisaparide (restricted availability) ▪ Delamanid[¶] ▪ Disopyramide[△] ▪ Dofetilide ▪ Dronedarone ▪ Haloperidol (IV) ▪ Ibutilide ▪ Ivosidenib 	<ul style="list-style-type: none"> ▪ Lenvatinib ▪ Levoketoconazole ▪ Methadone ▪ Mobocertinib ▪ Papavirine (intracoronary) ▪ Procainamide ▪ Quinidine ▪ Quinine 	<ul style="list-style-type: none"> ▪ Selpercatinib ▪ Sertindole[¶] ▪ Sotalol ▪ Terfenadine[◊] ▪ Vandetanib ▪ Vernakalant[¶] ▪ Ziprasidone 	Moderate risk				<ul style="list-style-type: none"> ▪ Amisulpride[¶] (oral)[§] ▪ Azithromycin ▪ Capecitabine ▪ Carbetocin[¶] ▪ Certinib ▪ Chloroquine ▪ Citalopram ▪ Clarithromycin ▪ Clofazimine ▪ Clomipramine[¥] 	<ul style="list-style-type: none"> ▪ Droperidol ▪ Encorafenib ▪ Entrectinib ▪ Erythromycin ▪ Escitalopram ▪ Etelcalcetide ▪ Fexinidazole ▪ Flecainide ▪ Flouxuridine ▪ Fluconazole 	<ul style="list-style-type: none"> ▪ Inotuzumab ozogamicin ▪ Isoflurane ▪ Levetiracetam ▪ Levofloxacin (systemic) ▪ Lofexidine ▪ Meglumine antimoniate ▪ Midostaurin ▪ Moxifloxacin ▪ Nilotinib 	<ul style="list-style-type: none"> ▪ Propafenone ▪ Propofol ▪ Quetiapine ▪ Quizartinib ▪ Ribociclib ▪ Risperidone ▪ Saquinavir ▪ Sevoflurane ▪ Sparfloxacin[¶] ▪ Sunitinib
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■ 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¥	■ Pimozide	
		■ Piperaquine	
		■ Probuconol◊	
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	■ Fostemsavir	■ Mirtazapine	■ Salmeterol
■ Arformoterol	■ Gadofosveset	■ Mizolastine	■ Sertraline
■ Artemether-lumefantrine	■ Glasdegib	■ Nelfinavir	■ Siponimod
■ Asenapine	■ Goserelin	■ Norfloxacin	■ Solifenacin
■ Atomoxetine	■ Granisetron	■ Nortriptyline¥	■ Sorafenib
■ Benperidol	■ Hydroxychloroquine (rare reports)	■ Ofloxacin (systemic)	■ Sulpiride
■ Bilastine¶	■ Hydroxyzine	■ Olodaterol	■ Tacrolimus (systemic)
■ Bosutinib	■ Iloperidone	■ Osilodrostat	■ Tamoxifen
■ Bromperidol	■ Indacaterol	■ Oxaliplatin	■ Telavancin
■ Buprenorphine†	■ Itraconazole	■ OzanimodΔΔ	■ Telithromycin
■ Buserelin	■ Ketoconazole (systemic)	■ Pacritinib	■ Teneligliptin
■ Ciprofloxacin (Systemic)	■ Lacidipine	■ Paliperidone	■ Tetrabenazine
■ Cocaine (Topical)	■ Lapaletinib	■ Panobinostat	■ Trazodone
■ Degarelix	■ Lefamulin	■ Pasireotide	■ Triclabendazole
■ Desipramine¥	■ Leuprolide	■ Pefloxacin	■ Triptorelin
■ Deutetrabenazine	■ Leuprolide-norethindrone	■ Periciazine¶	■ Tropisetron¶
■ Dexmedetomidine**	■ Levalbuterol	■ Pimavanserin	■ Vardenafil
■ Dolasetron	■ Levomethadone	■ Pipamperone	■ Vilanterol
■ Donepezil	■ Lithium	■ Pitolisant	■ Vinflunine
■ Efavirenz	■ Loperamide¶ in overdose	■ Ponesimod	■ Voclosporin
■ Eliglustat	■ Lopinavir	■ Primaquine	■ Vorinostat
■ Eribulin	■ Macimorelin	■ Promazine	■ Zuclopentixol
■ Ezogabine	■ Mefloquine	■ 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^[1,2]. 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.

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://crediblemeds.org/>.

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
<ul style="list-style-type: none"> ▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone* ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Omibitasvir-paritaprevir-ritonavir ▪ Omibitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Tucatinib ▪ Voriconazole 	<ul style="list-style-type: none"> ▪ Amiodarone¶ ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine¶ ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine¶ ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant¶ ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil 	<ul style="list-style-type: none"> ▪ Apalutamide ▪ Carbamazepine ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin) 	<ul style="list-style-type: none"> ▪ Bevacizumab ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone△ ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack◊ ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.^[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.^[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.^[1]

◊ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

Data from: Lexicomp Online (Lexi-Interact). Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.

References:

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* (January 2020) available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions>.
 2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.* Available at: FDA.gov website.
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Graphic 76992 Version 94.0

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

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

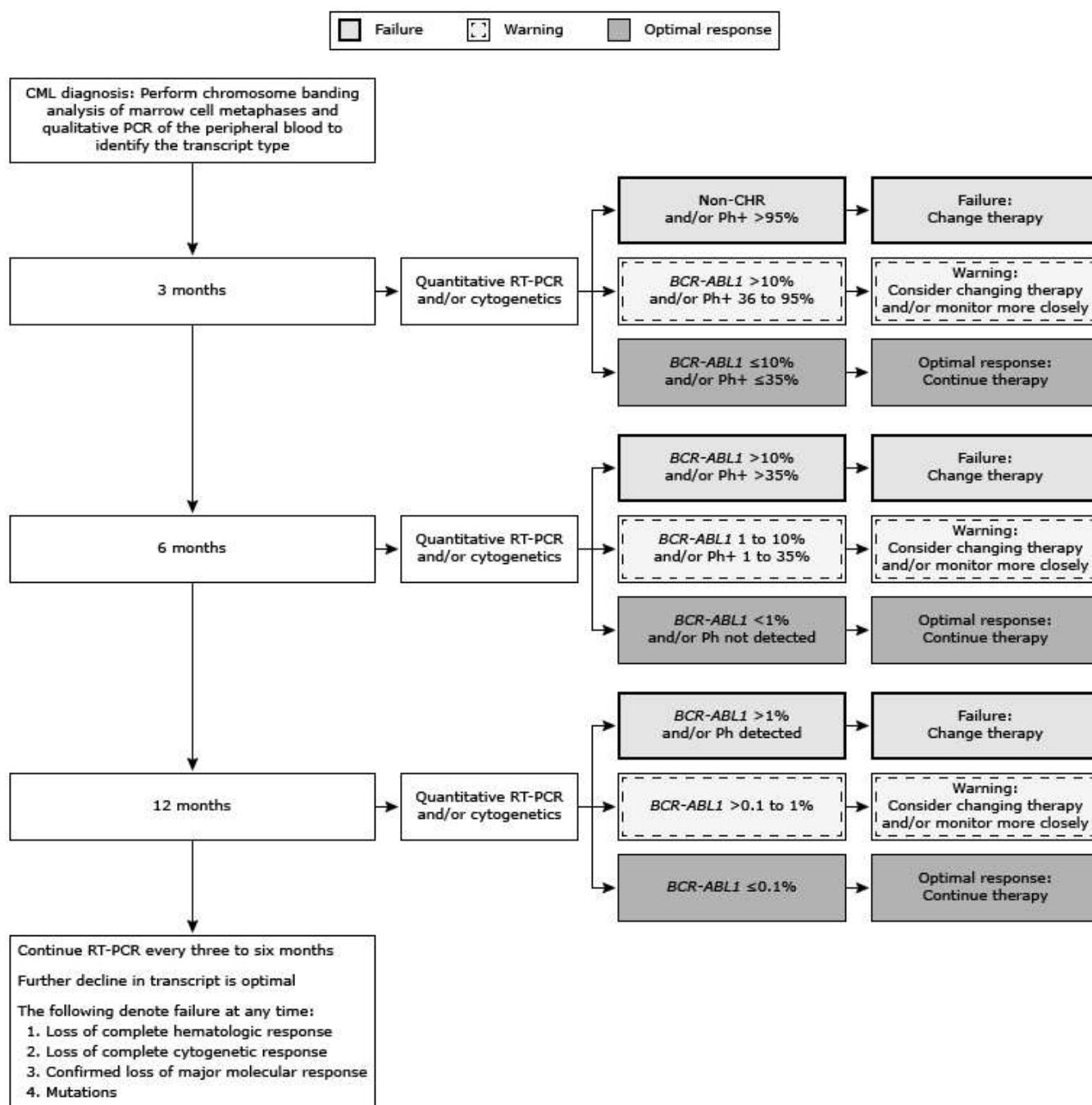
The definitions are the same for patients in chronic phase, accelerated phase, and blast crisis and apply also to second-line treatment, when first-line treatment was changed for intolerance. The response can be assessed with either a molecular or a cytogenetic test, but both are recommended whenever 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^{3.0} or better) is optimal for survival, but that a deeper response is likely to be required for a successful discontinuation of treatment.

NA: not applicable; MMR: BCR-ABL1 ≤0.1 percent = MR^{3.0} 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.

This research was originally published in Blood. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013; 122:872-84. Copyright © the American Society of Hematology.

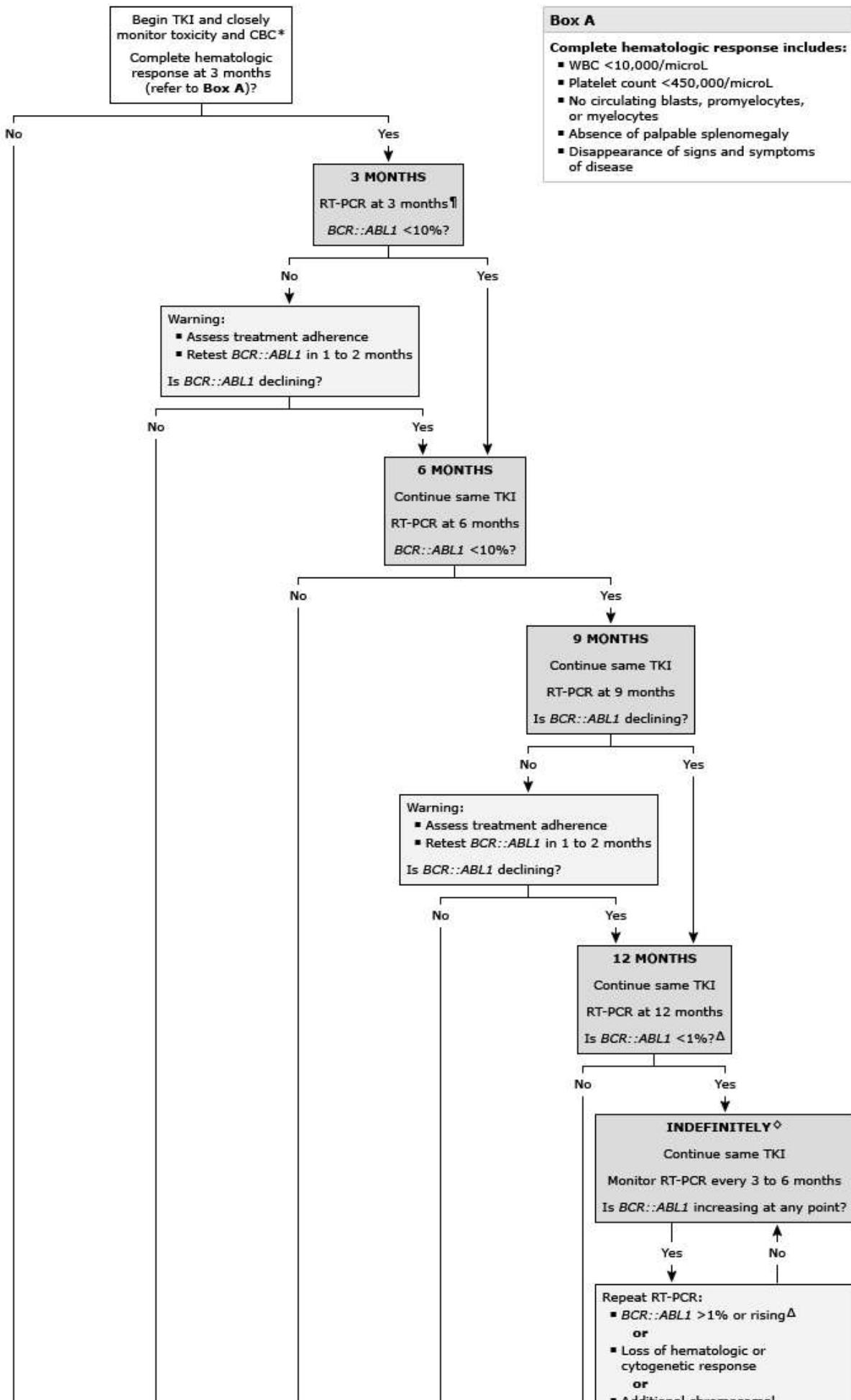
Algorithm for monitoring disease response to initial therapy in chronic myeloid leukemia (CML)

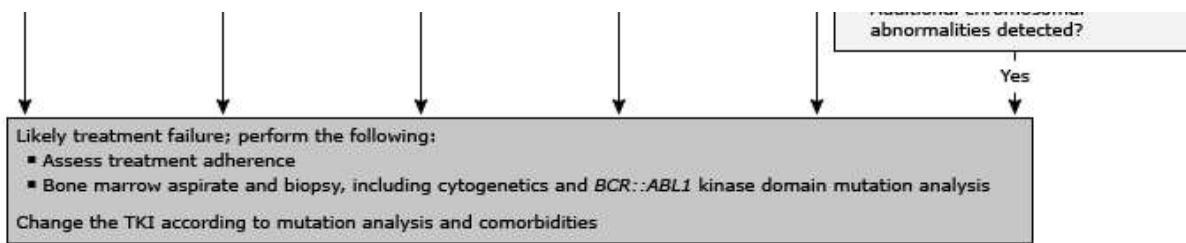


This algorithm provides an approach to monitoring patients with CML. Cytogenetics are the preferred method for assessment until a complete cytogenetic response is attained.

CML: chronic myeloid leukemia; PCR: polymerase chain reaction; Ph: Philadelphia chromosome; Ph+: Philadelphia chromosome positive; RT-PCR: reverse transcription polymerase chain reaction; CHR: complete hematologic response.

Monitoring response to initial therapy of chronic phase chronic myeloid leukemia (CML)





For RT-PCR values close to the thresholds in the algorithm, the study should be repeated within 1 to 2 months; importantly, the trend is more important than a single value for making treatment decisions. Changes of TKI should be avoided in response to early mild adverse effects, such as rash, nausea, or depression; a temporary TKI dose reduction or brief interruption may help evaluate the relation of such symptoms to the TKI. Significant or symptomatic cytopenias may be managed with transfusions for anemia, myeloid growth factors for neutropenia, and platelet transfusions or a TPO-R agonist for thrombocytopenia.

This algorithm should be used in conjunction with related UpToDate topics, which also discuss classification of CML, selection of an initial TKI, management of adverse effects, importance of treatment adherence, possible drug interactions, additional details of treatment monitoring and responses, and considerations for TKI discontinuation.

TKI: tyrosine kinase inhibitor; CBC: complete blood count and differential count; WBC: white blood cells; RT-PCR: reverse transcriptase polymerase chain reaction; TPO-R: thrombopoietin receptor agonist; FISH: fluorescence in situ hybridization.

* We generally obtain a CBC weekly for the first month of treatment, every two weeks in the second month, and as needed in the third month.

¶ In addition to RT-PCR, assessment of cytogenetic response by karyotype or FISH is encouraged, but not required, in the first year of treatment or until a complete cytogenetic response is achieved. Rising levels of *BCR::ABL1* at successive quarterly testing in the first year should be considered a "warning" and testing should be repeated in 1 to 2 months.

Δ Experts differ regarding the target molecular response (eg, <0.1% versus <1%).

◊ Selected patients may be considered for a trial of treatment-free remission; refer to related UpToDate topics for criteria and management.

Graphic 140486 Version 1.0

