

# Overview of the treatment of chronic myeloid leukemia

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## INTRODUCTION

Chronic myeloid leukemia (CML; previously called chronic myelogenous leukemia) is a myeloproliferative neoplasm (MPN), in which cells of the granulocytic lineage are the predominant proliferative component. CML is associated with the Philadelphia chromosome, t(9;22)(q34;q11), which creates a *BCR::ABL1* fusion gene (figure 1). This genetic abnormality encodes the constitutively active tyrosine kinase *BCR::ABL1*, which is essential to the development of CML and is the primary target for treatment of CML.

CML shares the following biologic features with the other MPNs, namely, polycythemia vera, essential thrombocythemia, and primary myelofibrosis (table 1) (see "Overview of the myeloproliferative neoplasms"):

- **Stem cell origin** – Clonal disorders that arise in a hematopoietic stem or early progenitor cell
- **Dysregulated proliferation** – Dysregulated production of a particular lineage of mature myeloid cells with fairly normal differentiation
- **Progression to acute leukemia** – Variable rates of progression to acute leukemia

An overview of treatment of CML is presented in this topic.

Clinical presentation, diagnosis, and initial treatment of CML are discussed separately. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia" and "Initial treatment of

chronic myeloid leukemia in chronic phase".)

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## DISEASE PHASES

Diagnostic criteria for CML and its disease phases are evolving [1-3]. The natural history of CML has been traditionally described as triphasic; however, some experts now view CML as biphasic process:

- **Chronic phase (CP)** – The most common clinical presentation of CML is CP, which is manifest as leukocytosis (with neutrophils in various stages of maturation), hypercellular bone marrow with marked granulocytic proliferation and few blasts (eg, <5 percent), with or without splenomegaly. CP CML is a relatively indolent disorder that is easily controlled with oral agents.
- **Advanced disease (accelerated phase [AP] and/or blast phase [BP])** – Together, AP and BP may be considered as a continuum of more aggressive CML. Advanced CML most often arises during treatment of CP CML. AP and BP are uncommon initial presentations of CML, but this is more likely in settings of limited access to medical care where diagnosis may be delayed.

Advanced disease is characterized by increasing blood/marrow blasts (AP: 10 to 19 percent; BP: ≥20 percent) and/or extramedullary collections of blasts. This is often accompanied by increasing splenomegaly, constitutional symptoms, worsening cytopenias, and/or genetic instability (eg, additional chromosomal abnormalities). Advanced disease may manifest as an acute leukemia, which can resemble acute myeloid leukemia (AML) or, less often, acute lymphoblastic leukemia. Compared with CP CML, advanced CML is considerably more difficult to control.

Evolving diagnostic criteria should be kept in mind when reviewing treatment outcomes. Diagnostic criteria for CML and its phases are discussed in greater detail separately. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia".)

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## PRETREATMENT EVALUATION

CML disease phase, prognostic score, and comorbid conditions should be determined before initiating treatment.

**Clinical/laboratory** — Clinical evaluation should assess comorbidities (eg, cardiovascular, pulmonary, kidney, pancreatic, or liver disease and diabetes) that may influence the choice of initial therapy and medications that may interact with tyrosine kinase inhibitors (TKIs) ( table 2 and table 3).

In addition to history and physical examination, the following studies should be obtained:

- **Hematology** – Complete blood count (CBC) with differential count.
- **Serum chemistries** – Electrolytes, glucose, liver function tests, kidney function tests, uric acid.
- **Cytogenetic and molecular testing** – Cytogenetic and molecular testing of marrow or blood:
  - **Cytogenetics** – Chromosome banding to confirm detection of the t(9;22) (Philadelphia chromosome [Ph]) rearrangement and to identify additional chromosomal abnormalities (ACA).
  - **Polymerase chain reaction (PCR)** – Quantitative PCR to establish a baseline value for *BCR::ABL1* rearrangement.
- **Viral testing** – Hepatitis B panel; there are rare cases of hepatitis B reactivation with treatment.
- **Electrocardiogram (EKG)** – Assess arrhythmias and QT interval.
- **Chest radiography** – Pleural effusions or parenchymal disease.

Diagnostic criteria for CML and discussion of pretreatment evaluation are discussed in greater detail separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase".)

**Prognostic score** — CML prognosis is estimated using one of the validated CML clinical scoring systems.

We favor the ELTS (EUTOS Long Term Survival) score, which is based on data from tyrosine kinase inhibitor (TKI)-treated patients (rather than non-TKI-based management) and uses simple hematologic data, spleen size, and age [4,5].

Validated CML clinical scoring systems ( table 4) are:

- ELTS (EUTOS Long Term Survival) score (calculator 1) [4]

- Sokal (calculator 2) [6]
- Euro (Hasford) [7]
- EUTOS (online calculator [8]) [9]

Details of CML prognostic models are presented separately. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Prognosis'.)

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## TREATMENT OVERVIEW

CML is associated with the Philadelphia chromosome (Ph), which refers to the t(9;22)(q34;q11) chromosomal translocation. This rearrangement creates a *BCR::ABL1* gene fusion, which encodes the constitutively active tyrosine kinase, *BCR::ABL1*. Because of the essential role of this genetic rearrangement in the generation and maintenance of CML, *BCR::ABL1* tyrosine kinase inhibitors (TKIs) play an important role in management of all phases of CML.

- **Goals of care** – The goals of care for patients with CML are to achieve clinical, cytogenetic, and molecular remission; maintain long-term disease control; and avoid progression to advanced disease (ie, accelerated phase [AP] or blast phase [BP]), while optimizing quality of life by limiting treatment-related toxicity.

Many patients and clinicians also consider achieving a treatment-free remission (TFR) an important goal. (See 'TKI discontinuation' below.)

Palliation of symptoms may be the goal for severely debilitated or frail patients.

- **Treatments** – Patients are treated with a *BCR::ABL1* TKI, unless there is a specific contraindication. Selection of a TKI is influenced by disease phase and comorbid conditions.
  - **Tyrosine kinase inhibitors** – TKIs are oral agents that are the preferred treatment for almost all newly-diagnosed patients with CML.

Selection of a TKI is guided by disease phase, CML risk score, adverse effects (AEs), and comorbid conditions. For patients with advanced disease, selection of a TKI is also influenced by *BCR::ABL1* mutations. (See 'Initial treatment' below.)

Individual TKIs are discussed below. (See 'Tyrosine kinase inhibitors (TKI)' below.)

- **Other agents** – Other medications can provide symptomatic relief for patients who cannot take a TKI (eg, pregnancy), who have intolerance/severe AEs with multiple TKIs, or who require additional symptomatic relief. Examples of other agents include interferon alfa, hydroxyurea, and/or cytotoxic agents (eg, cytarabine, busulfan). (See 'Other agents' below.)
- **Allogeneic hematopoietic cell transplantation (HCT)** – Allogeneic HCT refers to treatment with intensive chemotherapy and/or radiation therapy to reduce the burden of CML cells, followed by restoration of blood cell formation by infusion of hematopoietic stem/progenitor cells from another individual (donor). Allogeneic HCT can cure some patients with CML (with outcomes related to the phase of disease at transplantation), but it is associated with substantial short-term and long-term toxicity (including graft-versus-host disease [GVHD] and second cancers) and treatment-related mortality. HCT is reserved for patients with advanced disease. (See 'Hematopoietic cell transplantation' below.)

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## INITIAL TREATMENT

BCR::ABL1 tyrosine kinase inhibitors (TKIs) are the mainstay of treatment for all phases of CML and are used for initial treatment, unless there is a specific contraindication (eg, pregnancy).

The development of TKIs has been one of the most exhilarating stories in modern medicine. With the elucidation of BCR::ABL1 as the key molecular defect in CML came a more complete understanding of the underlying pathophysiology, culminating in development of these highly effective agents.

Initial treatment of CML is stratified according to disease phase (ie, chronic phase versus advanced disease) and prognostic score (ie, low/intermediate-risk versus high-risk), as described in the sections that follow.

Initial treatment of CML generally uses either imatinib or a second-generation (2G) TKI (ie, dasatinib, nilotinib, bosutinib). Other TKIs (ie, ponatinib, asciminib) are reserved for patients who have demonstrated resistance to other TKIs or with specific *BCR::ABL1* mutations (eg, T315I). (See 'Tyrosine kinase inhibitors (TKI)' below.)

Monitoring the response to TKI treatment is discussed below. (See 'Monitoring response' below.)

**Chronic phase (CP)** — For patients with CP CML, we stratify selection of a BCR::ABL1 TKI according to:

- **Prognostic score** – CML risk score (ie, low/intermediate-risk versus high-risk) ( table 4). (See 'Pretreatment evaluation' above.)
- **Other considerations** – Toxicity profile, comorbid illnesses, medications that may interact with TKIs ( table 2 and table 3), availability, cost, patient preference, and the weight the patient places on achieving a treatment-free remission (TFR).

All BCR::ABL1 TKIs are effective for initial treatment of CP CML. There is no significant difference in overall survival (OS) between patients who begin treatment with imatinib versus a 2G TKI (eg, dasatinib, nilotinib, bosutinib). However, compared with imatinib, 2G TKIs generally achieve faster and deeper remissions and have lower rates of progression to advanced phase CML.

Administration, adverse effects (AEs), and outcomes of individual TKIs are presented separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase".)

Hydroxyurea can provide urgent relief for some patients with extreme leukocytosis (eg, >100,000/microL) or who are severely symptomatic with splenomegaly or systemic symptoms [10]. Occasional patients are not candidates for treatment with a TKI (eg, initial diagnosis during pregnancy, due to potential teratogenicity). (See 'Other agents' below.)

Detailed discussion of management of CP CML is presented separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase".)

**Low/intermediate-risk CP CML** — For patients with low-risk or intermediate-risk CP CML ( table 4), the choice of a TKI is influenced by the importance assigned to achievement of a TFR:

- **TFR is an important goal** – For patients who consider TFR an important goal, we generally treat with a 2G TKI, rather than imatinib, based on faster, deeper remissions and lower rates of progression to advanced phase CML. Nevertheless, no studies have directly demonstrated greater success in achieving TFR using a 2G TKI.

Selection of a 2G TKI should consider the toxicity profile ( table 5), comorbid conditions, availability, cost, and patient preference. (See 'Tyrosine kinase inhibitors (TKI)' below.)

- **Less importance assigned to TFR** – For patients who do not consider TFR a high priority, treatment with either imatinib or a 2G TKI is acceptable. The choice of TKI for initial

treatment is based on toxicity profile (table 5), comorbid conditions, availability, cost, and patient preference. (See 'Tyrosine kinase inhibitors (TKI)' below.)

**High-risk score CP CML** — For patients with high-risk score CP CML (table 4), we favor initial treatment with a 2G TKI (ie, dasatinib, nilotinib, bosutinib) rather than imatinib because 2G TKIs are associated with a lower risk of progression to advanced disease (ie, accelerated phase [AP] or blast phase [BP]) CML.

None of the individual 2G TKIs has proven to be superior in this setting. Selection of a 2G TKI should consider the toxicity profile (table 5), comorbid conditions, availability, cost, and patient preference. (See 'Tyrosine kinase inhibitors (TKI)' below.)

**Advanced disease (accelerated phase/blast phase)** — We treat patients with advanced disease using a 2G TKI, ponatinib, or asciminib, rather than imatinib; selection of a specific TKI is guided by mutation analysis of *BCR::ABL1*, toxicity profile (table 5), and comorbidities. (See 'Tyrosine kinase inhibitors (TKI)' below.)

Patients with myeloid blast phase CML may also need cytotoxic chemotherapy, using regimens similar to those for acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), together with a TKI.

We initiate a search for a human leukocyte antigen (HLA)-matched donor at the time of diagnosis of advanced CML. A decision to proceed to allogeneic hematopoietic cell transplantation (HCT) is guided by the response to TKI therapy, medical fitness, and availability of a suitable donor. (See 'Hematopoietic cell transplantation' below.)

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## MONITORING RESPONSE

Response to tyrosine kinase inhibitor (TKI) therapy must be monitored on a regular schedule.

**Schedule** — Response to initial therapy is assessed according to hematologic, cytogenetic, and molecular criteria.

- **Hematology** – Monitor complete blood count (CBC) with differential every one to two weeks until a complete hematologic response (CHR) (table 6) is achieved, then repeat at times of cytogenetic or molecular testing, or as needed.

CHR is described below. (See 'Response milestones' below.)

- **Cytogenetics** – Monitoring the karyotype is used primarily for patients with atypical translocations (ie, rare or atypical *BCR::ABL1* transcripts that cannot be measured by quantitative polymerase chain reaction [PCR]), treatment failure or resistance (ie, to exclude additional chromosomal abnormalities), and with progression to advanced disease (ie, accelerated phase [AP] or blast phase [BP]). Fluorescence in situ hybridization (FISH) may be helpful for monitoring response in patients with atypical transcripts, but chromosome banding is needed for detection of additional chromosomal translocations. Note that monitoring the karyotype alone (ie, without molecular analysis) is not sufficiently sensitive to monitor response for most patients with CML.

Descriptions of cytogenetic response are provided below ( table 6). (See 'Response milestones' below.)

- **Reverse transcriptase polymerase chain reaction (RT-PCR)** – Monitor quantitative RT-PCR of blood every three months until achievement of major molecular response (MMR; ie, 3 log reduction of *BCR::ABL1*). Subsequent testing is performed every three to six months.

Descriptions of molecular response are provided below. (See 'Response milestones' below.)

Continued testing after MMR is important to assess eligibility for treatment discontinuation. (See 'TKI discontinuation' below.)

**Response criteria** — Response to TKI therapy ( table 6) is defined according to European LeukemiaNet guidelines [11,12].

**Hematologic response** — Complete hematologic response (CHR) is defined as [11,12]:

- White blood cell count (WBC) <10,000/microL
- No circulating immature myeloid cells and <5 percent basophils
- Platelet count <450,000/microL
- Spleen not palpable

**Cytogenetic response** — Cytogenetic response is assessed by chromosome banding of marrow metaphases with ≥20 metaphases analyzed. Chromosome banding generally requires a bone marrow aspirate sample.

Cytogenetic response is classified according to the percentage of Philadelphia chromosome positive (Ph+) cells ( table 6) [11,12]:

- **No cytogenetic response** – >95 percent Ph+ cells
- **Minimal cytogenetic response** – 66 to 95 percent Ph+ cells
- **Minor cytogenetic response** – 36 to 65 percent Ph+ cells
- **Major cytogenetic response** – 1 to 35 percent Ph+ cells
- **Complete cytogenetic response (CCyR)** – No Ph+ cells

For patients with an inadequate number of metaphases, CCyR can also be documented by FISH of blood interphase cell nuclei that demonstrate <1 percent *BCR::ABL1*-positive nuclei among ≥200 nuclei [13].

**Molecular response** — Molecular response is determined according to the International Scale (IS) as the ratio of *BCR::ABL1* transcripts to *ABL1* transcripts (or other housekeeping genes) and is expressed as *BCR::ABL1* percentage, on a log scale [11]. Results are presented as log reduction of *BCR::ABL1/ABL1* compared to a standardized baseline, which is defined as 100 percent (note that molecular response is not compared with the patient's own baseline value):

Key molecular response milestones are:

- **MR 3 (Major molecular response [MMR])** – 0.1 percent of baseline *BCR::ABL1/ABL1* (ie, ≥3 log reduction)
- **MR 4** – 0.01 percent
- **MR 4.5** – 0.0032 percent
- **MR 5** – 0.001 percent

**Response milestones** — Milestones for molecular response to therapy are used to determine if the current treatment should be continued (ie, Optimal response), changed (ie, Failure/resistance), or considered for continuation (ie, Warning) [11].

Molecular milestones of *BCR::ABL1* transcript levels are assessed at 3, 6, and 12 months. Additional testing may be needed if the response kinetics are uncertain or if toxicity/intolerance causes treatment interruptions or dose reductions.

In most circumstances, changes in a single PCR result alone should not be used to define treatment failure. However, a pattern of increasing PCR signal, with or without hematologic or cytogenetic evidence of failure, should trigger *BCR::ABL1* mutational analysis [11,14-16]. (See 'Evaluation at loss of response' below.)

The following definitions apply:

- **3 months** – Optimal ( $\leq 10$  percent); Warning ( $>10$  percent); Failure ( $>10$  percent, if confirmed within 1 to 3 months)
- **6 months** – Optimal ( $\leq 1$  percent); Warning ( $>1$  to  $10$  percent); Failure  $>10$  percent
- **12 months** – Optimal ( $\leq 0.1$  percent); Warning ( $>0.1$  to  $1$  percent); Failure  $>1$  percent
- **Any time** – Optimal ( $\leq 0.1$  percent); Warning ( $>0.1$  to  $1$  percent, with loss of MMR [ie,  $\leq 0.1$  percent]); Failure  $>1$  percent, resistance mutations, or acquisition of additional chromosomal abnormalities

Achieving MMR (ie,  $BCR::ABL1 \leq 0.1$  percent) within one year predicts a CML-specific survival close to 100 percent [11]. Prospective and retrospective studies that support use of milestone criteria for managing CML are presented separately [17-27]. (See "Initial treatment of chronic myeloid leukemia in chronic phase".)

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## TREATMENTS

**Tyrosine kinase inhibitors (TKI)** — TKIs are effective oral agents that target the  $BCR::ABL1$  tyrosine kinase.

Selection of a TKI is guided by disease phase (ie, chronic phase [CP] versus advanced disease) and CML risk score (ie, low/intermediate-risk versus high-risk) (table 4). Other considerations include side effect profile, comorbid illnesses, medications that may interact with TKIs (table 2 and table 3), availability, cost, patient preference/convenience, and importance assigned by a patient to achieving a treatment-free remission (TFR). (See 'Initial treatment' above.)

All TKIs are associated with common, generally mild toxicities (eg, rash, nausea, edema, fatigue, myalgias/arthritis) in the first months of treatment; most resolve spontaneously or can be controlled by dose adjustments. Management of these early adverse effects (AEs) is discussed separately. Interruption of TKI therapy has been associated with poor long-term outcomes. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Managing toxicity'.)

In addition, each TKI is associated with particular AEs (table 5):

- **Imatinib** – Muscle cramps, fatigue, edema, nausea, diarrhea.

- **Nilotinib** – Coronary, cerebral, and peripheral vascular disease; prolonged QTc interval; hyperglycemia; pancreatitis.
- **Dasatinib** – Pleural or pericardial effusion, pulmonary hypertension, prolonged QTc interval, platelet dysfunction.
- **Bosutinib** – Diarrhea, abnormal liver function, rash, pancreatitis.
- **Ponatinib** – Arterial and venous thrombosis, embolic events, liver toxicity.
- **Asciminib** – Pancreatitis, upper respiratory tract infection, musculoskeletal pain.

As examples of how we consider comorbidities and AEs in selecting a TKI for initial treatment of CML:

- **Heart disease or hyperglycemia** – For patients with arrhythmias, coronary artery disease, or hyperglycemia, we favor imatinib, bosutinib, or dasatinib.
- **Pancreatitis** – For patients with a history of pancreatitis we favor imatinib, or dasatinib.
- **Lung disease** – For patients with a history of lung disease or at risk for pleural effusion, we favor imatinib, nilotinib, or bosutinib.

Detailed discussion of selecting a TKI for initial treatment of CML is presented separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Choosing a TKI'.)

Dasatinib, nilotinib, bosutinib, and radotinib have been tested against imatinib in randomized, company-sponsored trials, but they have not been tested against each other. Comparisons among these and other clinical studies are difficult because of differences in protocols and methods of evaluation [28].

Imatinib, dasatinib, nilotinib, and bosutinib are approved for initial treatment of CML by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA); radotinib has been approved in South Korea only. Asciminib is approved for patients with CP CML previously treated with  $\geq 2$  TKIs or with T315I mutation. Ponatinib is approved for patients with CP CML with resistance or intolerance to  $\geq 2$  prior TKIs, advanced phase CML for which no other TKIs are indicated, and for patients with T315I-positive CML (CP or advanced disease).

**Other agents** — Other drugs can be used for treatment of CML in certain settings. None of these agents approaches the efficacy of TKIs, but they may be used when TKIs cannot be given safely (eg, pregnancy), to relieve symptoms or prevent complications while awaiting results of mutation analysis, or for managing TKI resistance.

Examples of settings in which non-TKI agents might be used include:

- **Hydroxyurea** – A short course of hydroxyurea (eg, 20 to 40 mg/kg/day, adjusted up or down to the nearest pill) [10] may be given to patients with significant leukocytosis (eg, >100,000/microL), systemic symptoms, or symptomatic splenomegaly while awaiting results from cytogenetic or molecular confirmation of the diagnosis of CML or for management of advanced phase CML while awaiting *BCR::ABL1* mutation analysis. The dose should be tapered as the white blood cell count decreases.
- **Interferon** – Interferon (IFN) alfa can be given to patients who are diagnosed with CML during 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. IFN alfa is considered safe during pregnancy. (See "Initial treatment of chronic myeloid leukemia in chronic phase".)
- **Omacetaxine mepesuccinate** – This agent, previously known as homoharringtonine, can be used for treatment of resistance and/or intolerance to ≥2 TKIs.

These and other agents (eg, cytarabine, busulfan) are mostly of historic interest, although they can benefit patients who are not candidates for transplantation and are intolerant of or refractory to treatment with TKIs.

**Hematopoietic cell transplantation** — Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment option for medically-fit patients with advanced disease (ie, accelerated phase [AP]/blast phase [BP]). HCT is occasionally offered for younger patients with chronic phase (CP) CML who have a suitable donor and are not responding adequately to TKI therapy. However, HCT is associated with significant early and late toxicity and an increased rate of early mortality.

A decision to proceed to allogeneic HCT must consider:

- **Medically eligible** – Eligibility for transplantation, based on age (eg, <70 years in many institutions) and medical fitness. (See "Determining eligibility for allogeneic hematopoietic cell transplantation".)
- **Suitable donor** – Donors may include a human leukocyte antigen (HLA)-matched related or unrelated donor, haploidentical related donor, or umbilical cord blood.

Selection of a donor, method for graft collection, and choice of a conditioning (preparative) regimen are discussed separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)

## TKI DISCONTINUATION

Treatment with a tyrosine kinase inhibitor (TKI) is generally continued indefinitely, as long as the drug is tolerated and treatment milestones are met. However, patients with a sustained, deep molecular response may seek TKI discontinuation because of toxicity, convenience, cost, a desire to become pregnant, or other reasons.

TKI discontinuation should take place only after meeting all criteria for treatment discontinuation including:

- Reliable use of the TKI for  $\geq 3$  years
- No prior resistance to a second-generation (2G) TKI that required switching to another agent
- Stable molecular response on repeated testing (ie, MR4; *BCR-ABL1*  $\leq 0.01$  percent)
- Access to a reliable quantitative polymerase chain reaction (PCR) test that can detect at least MR 4.5 and can provide results within two weeks

Details of criteria for treatment discontinuation, adverse effects of discontinuation, and outcomes are presented separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'TKI discontinuation for TFR'.)

## DISEASE RESISTANCE

Patients who appear to have resistant disease should be questioned carefully to assure that they are taking the tyrosine kinase inhibitor (TKI) at the recommended dose and schedule and avoiding medications or herbal supplements that may impair efficacy (table 2 and table 3).

Management of adverse effects of TKIs is discussed separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Managing toxicity'.)

**Evaluation at loss of response** — For patients who are reliably taking the TKI, yet do not achieve molecular milestones (ie, "Failure" or "Warning"), disease status must be re-evaluated. Response milestones are discussed above. (See 'Response milestones' above.)

For patients with suspected TKI resistance, testing includes:

- **Hematology** – Complete blood count with differential count
- **Bone marrow examination** – Including microscopy and cytogenetic testing to evaluate progression to advanced disease (ie, accelerated phase [AP] or blast phase [BP])
- **Mutation status** – *ABL1* kinase domain (KD) mutation analysis

**Treatment of disease resistance or drug intolerance** — Resistance to a TKI is usually detected when a patient with an initial response to a TKI loses that response. Approximately 40 to 50 percent of patients change from their initial TKI due to resistance or intolerance [29].

Management of TKI resistance is guided by *ABL1* KD mutation analysis.

The more common acquired *ABL1* KD mutations include:

- **T315I** – Resistant to all TKIs, except ponatinib and asciminib
- **Y253F** and **F359V** – Sensitive to dasatinib, bosutinib, ponatinib and asciminib, but resistant to imatinib and nilotinib
- **E255V** – Sensitive to dasatinib and asciminib, but resistant to bosutinib and nilotinib
- **F317L** – Sensitive to bosutinib, nilotinib, ponatinib and asciminib, but resistant to dasatinib
- **V299L** – Sensitive to imatinib, nilotinib, ponatinib and asciminib, but resistant to bosutinib and dasatinib

Omacetaxine mepesuccinate (previously known as homoharringtonine) may also be considered for treatment of TKI resistance.

Drug selection for treatment of TKI resistance is discussed separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)

Allogeneic hematopoietic cell transplantation (HCT) is an option for patients who progress to advanced disease (ie, accelerated phase or blast phase) who are resistant to multiple TKIs or are unable to tolerate a TKI . (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)

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## SOCIETY GUIDELINE LINKS

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

leukemia".)

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## INFORMATION FOR PATIENTS

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

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

- 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)" and "Patient education: Hematopoietic cell transplantation (bone marrow transplantation) (Beyond the Basics)")
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## SUMMARY

- **Description** – Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with the Philadelphia chromosome, t(9;22)(q34;q11), which creates a *BCR::ABL1* fusion gene (figure 1) and the constitutively active tyrosine kinase, BCR::ABL1.
- **Disease phases** – Diagnostic criteria for disease phases of CML are evolving. Briefly, CML disease phases can be described as follows:
  - **Chronic phase (CP)** – A relatively indolent condition with leukocytosis (that includes various stages of neutrophil maturation), hypercellular marrow, few blasts, with or without splenomegaly. CP CML is readily controlled with oral agents.
  - **Advanced disease** – Accelerated phase (AP) and blast phase (BP) can be considered a continuum of more aggressive CML that is unusual at initial presentation but arises more often during treatment of CP CML. Advanced disease is generally manifest with

increasing blasts, splenomegaly, constitutional symptoms, worsening cytopenias, and/or genetic instability.

- **Pretreatment evaluation** – Includes comorbid conditions (eg, heart, lung, kidney diseases), CML phase, and prognostic score.
- **Initial treatment** – BCR::ABL1 tyrosine kinase inhibitors (TKI) are the initial treatment of CML, unless contraindicated (eg, pregnancy). TKI choice is stratified by disease phase (ie, chronic phase versus advanced disease).
- **Treatment of CP** – Choice of TKI is based on CML risk score (table 4), toxicity, comorbidities, availability, cost, and patient preference.
  - **Low/intermediate risk** – Stratified by importance of achieving treatment-free remission (TFR) (see 'Low/intermediate-risk CP CML' above):
    - **TFR is an important goal** – For patients who consider TFR an important goal, we generally treat with a second generation (2G) TKI (eg, dasatinib, nilotinib, bosutinib), rather than imatinib.
    - **TFR is less important** – If a TFR is not a high priority, treatment with imatinib or a 2G TKI is acceptable.
  - **High risk** – We favor initial treatment with a 2G TKI, rather than imatinib. Ponatinib or asciminib should be given if *BCR::ABL1* T315I mutation is present. (See 'High-risk score CP CML' above.)
- **Treatment of advanced disease** – We favor treatment with a 2G TKI, ponatinib, or asciminib, rather than imatinib; selection of a TKI is based on mutation analysis, toxicities, and comorbidities. (See 'Advanced disease (accelerated phase/blast phase' above.)
- **Response** – The schedule for monitoring hematologic, cytogenetic, and molecular responses and various treatment milestones are discussed above. (See 'Monitoring response' above.)
- **TKIs** – TKI selection is guided by disease phase, CML risk score (table 4), side effect profile, comorbid illnesses, availability, cost, and patient preferences. (See 'Tyrosine kinase inhibitors (TKI)' above.)
- **Other treatments** – Hydroxyurea, interferons, and other agents are used occasionally. (See 'Other agents' above.)

- **Transplantation** – Allogeneic hematopoietic cell transplantation is a consideration for medically-fit patients with a suitable donor who have advanced disease or intolerance/resistance to all TKIs. (See 'Hematopoietic cell transplantation' above.)
  - **TKI discontinuation** – Selected patients who achieve a sustained, deep remission may be candidates for TKI discontinuation, as discussed above. (See 'TKI discontinuation' above.)
  - **Disease resistance** – For patients who are taking the TKI properly, evaluation for disease progression or emergence of *BCR::ABL1* mutation resistance and selection of an alternative TKI or other treatment is discussed above. (See 'Disease resistance' above.)
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## ACKNOWLEDGMENT

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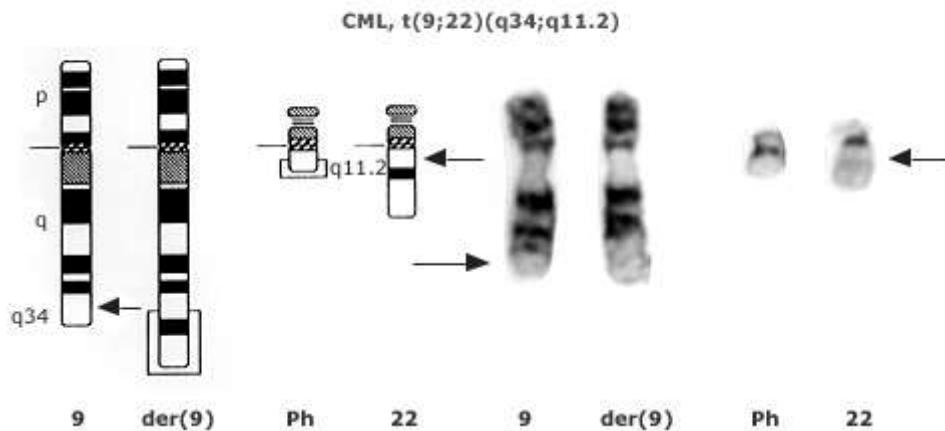
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## GRAPHICS

### The Philadelphia chromosome in chronic myeloid leukemia



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

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Courtesy of Athena Cherry, PhD.

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Graphic 62227 Version 2.0

# **World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia**

## **Myeloproliferative neoplasms (MPN)**

Chronic myeloid leukemia (CML), *BCR-ABL1*<sup>+</sup>

Chronic neutrophilic leukemia (CNL)

Polycythemia vera (PV)

Primary myelofibrosis (PMF)

- PMF, prefibrotic/early stage
- PMF, overt fibrotic stage

Essential thrombocythemia (ET)

Chronic eosinophilic leukemia, not otherwise specified (NOS)

MPN, unclassifiable

## **Mastocytosis**

### **Myeloid/Lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2***

Myeloid/Lymphoid neoplasms with *PDGFRA* rearrangement

Myeloid/Lymphoid neoplasms with *PDGFRB* rearrangement

Myeloid/Lymphoid neoplasms with *FGFR1* rearrangement

## **Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN)**

Chronic myelomonocytic leukemia (CMML)

Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*<sup>-</sup>

Juvenile myelomonocytic leukemia (JMML)

MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

MDS/MPN, unclassifiable

## **Myelodysplastic syndromes (MDS)**

MDS with single lineage dysplasia

MDS with ring sideroblasts (MDS-RS)

- MDS-RS and single lineage dysplasia
- MDS-RS and multilineage dysplasia

MDS with multilineage dysplasia

MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
<b>Myeloid neoplasms with germ line predisposition</b>
<b>Acute myeloid leukemia (AML) and related neoplasms</b>
AML with recurrent genetic abnormalities
■ AML with t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i>
■ AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i>
■ APL with <i>PML-RARA</i>
■ AML with t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i>
■ AML with t(6;9)(p23;q34.1); <i>DEK-NUP214</i>
■ AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM</i>
■ AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); <i>RBM15-MKL1</i>
■ AML with mutated <i>NPM1</i>
■ AML with biallelic mutations of <i>CEBPA</i>
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
■ AML with minimal differentiation
■ AML without maturation
■ AML with maturation
■ Acute myelomonocytic leukemia
■ Acute monoblastic/monocytic leukemia
■ Pure erythroid leukemia
■ Acute megakaryoblastic leukemia
■ Acute basophilic leukemia
■ Acute panmyelosis with myelofibrosis
Myeloid sarcoma

## Myeloid proliferations related to Down syndrome

- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia associated with Down syndrome

## Blastic plasmacytoid dendritic cell neoplasm

### Acute leukemias of ambiguous lineage

Acute undifferentiated leukemia

Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2);*BCR-ABL1*

MPAL with t(v;11q23.3); *KMT2A* rearranged

MPAL, B/myeloid, NOS

MPAL, T/myeloid, NOS

## B-lymphoblastic leukemia/lymphoma

B-lymphoblastic leukemia/lymphoma, NOS

B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*

B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged

B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1);*ETV6-RUNX1*

B-lymphoblastic leukemia/lymphoma with hyperdiploidy

B-lymphoblastic leukemia/lymphoma with hypodiploidy

B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*

B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*

B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like\*

B-lymphoblastic leukemia/lymphoma with iAMP21\*

## T-lymphoblastic leukemia/lymphoma

\* Provisional entity.

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

<b>Congenital</b>			
<ul style="list-style-type: none"> <li>▪ Jervell and Lange-Nielsen syndrome (including "channelopathies")</li> <li>▪ Romano-Ward syndrome</li> <li>▪ Idiopathic</li> </ul>			
<b>Acquired</b>			
<b>Metabolic disorders</b> <ul style="list-style-type: none"> <li>▪ Hypokalemia</li> <li>▪ Hypomagnesemia</li> <li>▪ Hypocalcemia</li> <li>▪ Starvation</li> <li>▪ Anorexia nervosa</li> <li>▪ Liquid protein diets</li> <li>▪ Hypothyroidism</li> </ul> <b>Bradyarrhythmias</b> <ul style="list-style-type: none"> <li>▪ Sinus node dysfunction</li> <li>▪ AV block: Second or third degree</li> </ul>	<b>Other factors</b> <ul style="list-style-type: none"> <li>▪ Myocardial ischemia or infarction, especially with prominent T-wave inversions</li> <li>▪ Intracranial disease</li> <li>▪ HIV infection</li> <li>▪ Hypothermia</li> <li>▪ Toxic exposure: Organophosphate insecticides</li> </ul>	<b>Androgen deprivation therapy</b> <ul style="list-style-type: none"> <li>▪ GnRH agonist/antagonist therapy</li> <li>▪ Bilateral surgical orchectomy</li> </ul> <b>Diuretic therapy</b> via electrolyte disorders particularly hypokalemia and hypomagnesemia	<b>Herbs</b> <ul style="list-style-type: none"> <li>▪ Cinchona (contains quinine), iboga (ibogaine), licorice extract in overuse via electrolyte disturbances</li> </ul>
<b>Medications*</b>			
<b>High risk</b>			
<ul style="list-style-type: none"> <li>▪ Adagrasib</li> <li>▪ Ajmaline<sup>¶</sup></li> <li>▪ Amiodarone<sup>Δ</sup></li> <li>▪ Arsenic trioxide</li> <li>▪ Astemizole<sup>◊</sup></li> <li>▪ Bedaquiline</li> <li>▪ Bepridil<sup>◊</sup></li> <li>▪ Chlorpromazine</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cisaparide (restricted availability)</li> <li>▪ Delamanid<sup>¶</sup></li> <li>▪ Disopyramide<sup>Δ</sup></li> <li>▪ Dofetilide</li> <li>▪ Dronedarone</li> <li>▪ Haloperidol (IV)</li> <li>▪ Ibutilide</li> <li>▪ Ivosidenib</li> </ul>	<ul style="list-style-type: none"> <li>▪ Lenvatinib</li> <li>▪ Levoketoconazole</li> <li>▪ Methadone</li> <li>▪ Mobocertinib</li> <li>▪ Papavirine (intracoronary)</li> <li>▪ Procainamide</li> <li>▪ Quinidine</li> <li>▪ Quinine</li> </ul>	<ul style="list-style-type: none"> <li>▪ Selpercatinib</li> <li>▪ Sertindole<sup>¶</sup></li> <li>▪ Sotalol</li> <li>▪ Terfenadine<sup>◊</sup></li> <li>▪ Vandetanib</li> <li>▪ Vernakalant<sup>¶</sup></li> <li>▪ Ziprasidone</li> </ul>
<b>Moderate risk</b>			
<ul style="list-style-type: none"> <li>▪ Amisulpride<sup>¶</sup> (oral)<sup>§</sup></li> <li>▪ Azithromycin</li> <li>▪ Capecitabine</li> <li>▪ Carbetocin<sup>¶</sup></li> </ul>	<ul style="list-style-type: none"> <li>▪ Droperidol</li> <li>▪ Encorafenib</li> <li>▪ Entrectinib</li> <li>▪ Erythromycin</li> </ul>	<ul style="list-style-type: none"> <li>▪ Inotuzumab ozogamicin</li> <li>▪ Isoflurane</li> <li>▪ Levetiracetam</li> </ul>	<ul style="list-style-type: none"> <li>▪ Propafenone</li> <li>▪ Propofol</li> <li>▪ Quetiapine</li> <li>▪ Quizartinib</li> </ul>

■ Certinib	■ Escitalopram	■ Levofloxacin (systemic)	■ Ribociclib
■ Chloroquine	■ Etelcalcetide	■ Lofexidine	■ Risperidone
■ Citalopram	■ Fexinidazole	■ Meglumine antimoniate	■ Saquinavir
■ Clarithromycin	■ Flecainide	■ Midostaurin	■ Sevoflurane
■ Clofazimine	■ Floxuridine	■ Moxifloxacin	■ Sparfloxacin¶
■ Clomipramine¥	■ Fluconazole	■ Nilotinib	■ Sunitinib
■ Clozapine	■ Fluorouracil (systemic)	■ Olanzapine	■ Tegafur¶
■ Crizotinib	■ Flupentixol¶	■ Ondansetron (IV > oral)	■ Terbutaline
■ Dabrafenib	■ Gabobenate dimeglumine	■ Osimertinib	■ Thioridazine
■ Dasatinib	■ Gemifloxacin¶	■ Oxytocin	■ Toremifene
■ Deslurane	■ Gilteritinib	■ Pazopanib	■ Vemurafenib
■ Domperidone¶	■ Halofantrine	■ Pentamidine	■ Voriconazole
■ Doxepin¥	■ Haloperidol (oral)	■ Pilsicainide◊	
■ Doxifluridine¶	■ Imipramine¥	■ Pimozone	
		■ Piperazine	
		■ Probucol◊	

### Low risk‡

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

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

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

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

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

¶ Not available in the United States.

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

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

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

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

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

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

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

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

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

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

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*Data from:*

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

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

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

- 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.<sup>[1,2]</sup> 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.
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\* 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.<sup>[1]</sup>

Δ Classified as a weak inducer of CYP3A4 according to FDA system.<sup>[1]</sup>

◊ 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.

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*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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## Prognostic scoring systems for newly diagnosed chronic myeloid leukemia\*

Scoring system	Calculator Link	Risk groups
EUTOS score <sup>[1]</sup>	<a href="http://www.leukemia-net.org/content/leukemias/cml/eutos_score/">www.leukemia-net.org/content/leukemias/cml/eutos_score/</a>	Low risk, high risk
Euro (Hasford) score <sup>[2]</sup>	<a href="http://www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/">www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/</a>	Low risk, intermediate risk, high risk
Sokal score <sup>[3]</sup>	<a href="http://www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/">www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/</a>	Low risk, intermediate risk, high risk
The EUTOS long-term survival score (ELTS) <sup>[4]</sup>	<a href="http://www.leukemia-net.org/content/leukemias/cml/elts_score/">www.leukemia-net.org/content/leukemias/cml/elts_score/</a>	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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### References:

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

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

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

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

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## **Definitions of hematologic, cytogenetic, and molecular response in chronic myeloid leukemia<sup>[1,2]</sup>**

<b>Response by type</b>	<b>Definitions</b>
<b>Hematologic</b>	
Complete	WBC $<10 \times 10^9/L$
	Basophils $<5\%$
	No myelocytes, promyelocytes, myeloblasts in the differential
	Platelet count $<450 \times 10^9/L$
	Spleen nonpalpable
<b>Cytogenetic*</b>	
Major	Complete: No Ph+ metaphases or $<1\%$ BCR::ABL1-positive nuclei of $\geq 200$ nuclei on FISH
	Partial: 1 to 35% Ph+ metaphases
Minor	36 to 65% Ph+ metaphases

Minimal	66 to 95% Ph+ metaphases
None	>95% Ph+ metaphases
<b>Molecular¶</b>	
MR <sup>4.5</sup>	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> (or other housekeeping genes) ≤0.0032% ( $\geq 4.5$ log reduction) on the international scale (IS) <b>or</b> Undetectable disease in cDNA with $\geq 32,000$ <i>ABL1</i> transcripts
MR <sup>4</sup>	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> ≤0.01% ( $\geq 4$ log reduction) on the IS <b>or</b> Undetectable disease in cDNA with $\geq 10,000$ <i>ABL1</i> transcripts
MR <sup>3</sup>	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> (or other housekeeping genes) ≤0.1% ( $\geq 3$ log reduction) on the IS

WBC: white blood cell; Ph+: Philadelphia chromosome positive; FISH: fluorescence in situ hybridization; IS: international scale.

\* Chromosome banding analysis of  $\geq 20$  bone marrow cell metaphases is necessary to determine the degree of cytogenetic response. If marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCyR may be based on interphase fluorescence in situ hybridization of blood cells, provided that it is performed with *BCR::ABL1* extrasignal, dual color, dual fusion, or in situ hybridization probes, and that  $\geq 200$  nuclei are scored.

¶ Molecular responses are, in general, reported on the evaluation of blood, not marrow samples. For a standardized assessment of the MoIR, the conversion of each laboratory datum to the international scale (IS) is recommended, to correct for the variability of the assays in different laboratories. To allow for intra-laboratory variations, a fluctuation of less than one log requires confirmation.

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Data from:

1. Baccarani M, Cortes J, Pane F, et al. *Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet*. *J Clin Oncol* 2009; 27:6041.
  2. Baccarani M, Deininger MW, Rosti G, et al. *European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013*. *Blood* 2013; 122:872.
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