

Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy

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

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

This topic last updated: **Feb 17, 2022**.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with the Philadelphia chromosome t(9;22)(q34;q11), resulting in the *BCR::ABL1* fusion gene. This genetic abnormality results in the formation of a unique gene product (BCR::ABL1), which is a constitutively active tyrosine kinase. It is this deregulated tyrosine kinase that is implicated in the development of CML. (See "Molecular genetics of chronic myeloid leukemia".)

The majority of patients with CML present in a relatively indolent phase termed chronic phase and are treated initially with a *BCR::ABL1* tyrosine kinase inhibitor (TKI), such as imatinib, dasatinib, or nilotinib. Side effects are generally mild, but there are some patients who must discontinue the drug due to intolerance. In addition, second line therapy is required for the patient who has a suboptimal response (primary resistance) or relapses after an initial response (secondary resistance) to a TKI.

The treatment of patients with chronic phase CML who are intolerant of or have a primary or secondary resistance to a TKI will be reviewed here. The initial treatment of chronic phase CML and specific details regarding the pharmacology of TKIs are discussed separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase" and "Overview of the treatment of chronic myeloid leukemia" and "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Tyrosine kinase inhibitor selection'.)

DEFINING INTOLERANCE AND RESISTANCE

Intolerance — Long-term studies of BCR::ABL1 tyrosine kinase inhibitors (TKIs) have shown that side effects are usually mild and most patients can continue treatment without interruption. When more severe symptoms do develop, the majority resolve rapidly within a few days after stopping the TKI for a brief "drug holiday." Often, the drug can then be restarted at the same dose without a recurrence of the side effects. Fewer than 5 percent of patients treated with a TKI will be unable to tolerate long term treatment. The side effects of TKIs and their management are discussed in detail separately. (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Tyrosine kinase inhibitor selection'.)

While the TKIs have some side effect profiles in common, there are some notable variations. Common side effects include myelosuppression, gastrointestinal complaints, fatigue, headache, rash, and peripheral and periorbital edema (most notably with imatinib). Imatinib has been rarely associated with severe heart failure. Dasatinib may cause pleural effusions and rarely pulmonary hypertension, as well as gastrointestinal bleeding (probably related to an effect on platelet function). Dasatinib and nilotinib are associated with QT prolongation. Nilotinib can occasionally cause pancreatitis. Bosutinib can cause transient elevations of transaminases and significant diarrhea during the first one to two months of treatment.

Myelosuppression is uncommon after patients achieve remission, but neutropenia, thrombocytopenia, and anemia can occur during the initial treatment period until the marrow repopulates with normal hematopoietic cells. Some side effects, such as severe recurrent rash or hepatotoxicity, necessitate permanent discontinuation of therapy while others, as mentioned above, require only a brief "drug holiday."

There is no universal definition of intolerance. In general, we consider a patient intolerant when a grade 3 or 4 nonhematologic toxicity recurs despite appropriate dose reductions and optimal symptomatic management [1]. However, since these drugs must be taken daily for many years, even grade 1 or 2 toxicities may be considered intolerable by some patients, sometimes leading to poor adherence to treatment. Grading of toxicities is based on the United States National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [2].

Resistance — Resistance to treatment is divided into two categories: primary and secondary [3]. Primary resistance is when a TKI fails to achieve a desired response; this occurs in up to 25 percent of patients with chronic phase CML treated with imatinib (table 1 and table 2) [4].

Secondary resistance refers to relapse following an initial response to a TKI. The occurrence of secondary resistance has been estimated at approximately 8 percent at two years for patients

in chronic phase treated with imatinib [5-8].

Patients who appear to have resistant disease should be questioned carefully to assure that they are taking the TKI at the recommended dose and schedule and avoiding other medications or herbal supplements which may impair efficacy [9]. A study employing an electronic device to monitor compliance with imatinib therapy in 87 patients with CML in stable complete cytogenetic response on imatinib reported that compliance was an independent predictor of major molecular response (MMR) [10]. Patients with ≥90 percent compliance had a significantly higher rate of MMR at six years (95 versus 28 percent). No patients with compliance ≤80 percent attained a MMR. Compliance appeared to decrease among patients who had their imatinib dose escalated. Compliance also appears to be lower among patients with higher medication co-payments [11]. Imatinib blood levels can and should be measured if there are questions about an individual's compliance with the medication [12-15]. Plasma trough concentrations <1000 ng/mL are associated with higher rates of disease progression [16,17].

If resistance is identified, the disease phase should be re-evaluated using a complete blood count with differential and a bone marrow biopsy with cytogenetic testing. In addition, mutational analysis of *BCR::ABL1* should be performed. A newly acquired mutation in *BCR::ABL1* may trigger a change in treatment (eg, dose increase, change to another TKI, hematopoietic cell transplantation) depending upon the type of mutation found. Specific details on disease phase and mutational analysis are presented separately. (See "Overview of the treatment of chronic myeloid leukemia", section on 'Pretreatment evaluation'.)

Patients found to be in accelerated phase or blast crisis at the time of identification of TKI resistance are treated differently than those in chronic phase. This is discussed in detail separately. (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment" and "Treatment of chronic myeloid leukemia in blast crisis".)

INITIAL MANAGEMENT

Patients whose CML is resistant to any of the tyrosine kinase inhibitors (TKIs) should have evaluation of blood or bone marrow for the presence of *BCR::ABL1* kinase mutations. Such mutations can be identified in approximately 40 percent of such individuals and the sensitivity pattern of particular mutations can suggest the use of which TKI to use subsequently (figure 1). In addition, evaluation of the possibility of allogeneic hematopoietic cell transplantation (HCT) should be done, because "second line" treatment is not uniformly successful. Eligibility criteria for allogeneic HCT vary by institution. Patients are often excluded based on age (>70 years old), uncontrolled infection, cardiac, pulmonary, liver or renal

dysfunction, and/or psychosocial variables. Patients who are not candidates for HCT are treated almost exclusively with second generation TKIs. Trials that support the use of second generation TKIs in patients with intolerance or resistance to an initial TKI are discussed below. (See 'Dasatinib' below and 'Nilotinib' below and 'Bosutinib' below.)

Treatment with a second generation TKI (dasatinib, nilotinib, bosutinib) is the preferred approach for those patients for whom imatinib therapy is not successful. Approximately half of patients in chronic phase CML initially treated with imatinib will attain a durable complete cytogenetic response (CCyR) with a second generation TKI [18]. The response rates for patients not responding to initial treatment with dasatinib or nilotinib are less well defined but are considerably lower. Allogeneic HCT is usually reserved for those patients who have failed to respond to two or more TKIs.

Note that patients whose CML harbors the *BCR::ABL1* T315I mutation generally respond only to ponatinib, but not to other TKIs. Management in this setting is discussed below. (See 'T315I mutation' below.)

Choice of TKI — There are no randomized trials that have directly compared the efficacy of second generation TKIs in patients with chronic phase CML who experience failure of an initial TKI. Phase II studies in this population suggest that they have similar efficacy. Response rates are generally higher in patients who were switched due to intolerance compared with those switched due to resistance.

Dasatinib, nilotinib, and bosutinib can be used for most patients with intolerance or resistance to imatinib, with the choice sometimes determined by the presence and type of *BCR::ABL1* kinase mutation, if present. Importantly, patients with the *BCR::ABL1* T315I mutation only rarely respond to second generation TKIs; treatment with ponatinib is preferred in that setting.

Absence of BCR::ABL1 kinase mutations — The choice of second generation TKI for a patient without a *BCR::ABL1* mutation is based on the side effect profiles and knowledge of comorbid conditions in an individual patient (table 3). As examples:

- Dasatinib might be preferred in a patient with a history of pancreatitis, elevated bilirubin, or hyperglycemia, while nilotinib might be chosen for a patient with a history of pleural or pericardial disease or effusions.
- Dasatinib crosses the blood-brain barrier and would therefore be preferred in patients with central nervous system involvement at relapse [19].

- Since both dasatinib and nilotinib can result in QT prolongation, they should be avoided in patients with baseline QT prolongation that cannot be normalized. Attempts to normalize the QT interval include correction of possible electrolyte imbalances or discontinuation of other medications that may have affected the QT interval. Bosutinib is not known to prolong the QT interval.

The side effects from the second generation TKIs differ from imatinib toxicities and patients who are intolerant of imatinib generally tolerate another TKI without recurrence of the imatinib induced toxicities [20]. In the future, the choice of TKI may be influenced by the presence of a particular *BCR::ABL1* mutation that is more sensitive to one drug or another (figure 1) [21-23].

Increasing the dose of imatinib to 800 mg per day is another option for patients for whom 400 mg of imatinib fails due to resistance, but who are still able to tolerate imatinib. However, one randomized trial demonstrated higher response rates in patients treated with dasatinib compared with those whose imatinib dose was increased from 600 to 800 mg/day [24]. (See 'Increased dose imatinib' below.)

T315I mutation — In the setting of *BCR::ABL1* T315I mutation, we start treatment with ponatinib and simultaneously initiate evaluation for allogeneic HCT. (See 'Ponatinib' below and 'T315I mutation' below.)

We closely monitor the patient's cytogenetic and molecular status while administering ponatinib and titrate ponatinib to the lowest dose that maintains a cytogenetic response, in an attempt to diminish the incidence of cardiovascular side effects. We proceed with allogeneic HCT if complete cytogenetic remission is not achieved. Options for patients who are ineligible for HCT include treatment with omacetaxine, a chemotherapeutic regimen, or a clinical trial of an investigational agent.

Dasatinib — Three studies have evaluated the efficacy of dasatinib in patients in chronic phase CML with resistance or intolerance to prior therapy. The reported hematologic and major cytogenetic response (MCyR) rates were approximately 90 and 60 percent, respectively. These rates are comparable to those observed with nilotinib. Doses approved by the US Food and Drug Administration include both 70 mg twice daily and 100 mg once daily. The latter appears to have equal efficacy but less toxicity [25]. Detailed information on drug toxicity and management of side effects is discussed separately. (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Dasatinib'.)

The following are the largest studies that have evaluated dasatinib in this setting:

- A phase 2 study examined the use of dasatinib 70 mg twice daily in 186 chronic phase CML patients with imatinib resistance (73 percent) or intolerance [26]. The following results were reported at a median follow-up of eight months:
 - Complete hematologic response (CHR) was seen in 90 percent of patients. MCyR were seen in 39 and 80 percent of patients who were imatinib-resistant or intolerant, respectively.

- Dasatinib was well tolerated and only 9 percent of patients had to discontinue therapy due to adverse events. Grade 3/4 side effects included leukopenia (25 percent), neutropenia (49 percent), thrombocytopenia (47 percent), and anemia (22 percent). Six percent of patients developed grade 3/4 pleural effusions.

Extended follow-up of this trial included data from 387 patients followed for a median of 15 months [27]. Among patients with imatinib resistance, rates of CHR, MCyR, and CCyR were 90, 52, and 40 percent, respectively. Among patients with imatinib intolerance, these same levels of response were seen in 94, 80, and 75 percent, respectively. The median duration of response was not reached at 18 months. Among those who achieved a CHR, subsequent disease progression was seen in 9 and 3 percent of patients with imatinib resistance or intolerance, respectively.

- A phase 3 study investigated different dosing schedules of dasatinib in 670 patients with chronic phase CML resistant (74 percent) or intolerant to imatinib [25]. Patients were randomly assigned to four dosing strategies (50 mg twice daily, 100 mg daily, 70 mg twice daily, or 140 mg daily). The following results were noted at one-year follow-up:
 - There was no significant difference in CHR or MCyR rates among the four treatment arms. CHR was achieved in 86 to 92 percent of patients and CCyR was achieved in 41 to 45 percent of patients.
 - When compared with 70 mg twice daily, 100 mg daily dosing resulted in significantly less grade 3/4 thrombocytopenia, fewer pleural effusions, fewer dose reductions or interruptions, and fewer discontinuations due to toxicity.
 - Further follow-up of the patients taking 100 mg daily reported that 31 percent of patients continued dasatinib for at least six years with estimated six-year progression-free and overall survival rates of 49 and 71 percent, respectively [28].
- A randomized phase II trial showed superior response rates with dasatinib compared with increased dose imatinib in patients who had failed imatinib therapy [24]. (See 'Increased

dose imatinib' below.)

In aggregate, these studies support the use of dasatinib for the treatment of non-transplant candidates with chronic phase CML after the failure of imatinib therapy. Dasatinib can also be incorporated into the treatment of such patients who are candidates for HCT. (See 'Patients eligible for HCT' below.)

Cytogenetic response appears to correlate with survival. Dasatinib does not have activity in the highly resistant *BCR::ABL1* T315I mutation and has limited activity against the F317L mutation [3,29,30]. Despite this, in a review of three trials of dasatinib in patients with chronic phase CML who were resistant to, or intolerant of, imatinib, dasatinib was an effective treatment for the majority of patients with CML in chronic phase who developed an imatinib-resistant *BCR::ABL1* mutation [30].

The use of dasatinib in previously untreated disease and the relationship between cytogenetic response and survival are discussed elsewhere. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Dasatinib'.)

Nilotinib — Uncontrolled prospective trials have evaluated the effectiveness of nilotinib in imatinib resistant or intolerant patients. Nilotinib results in complete hematologic and cytogenetic response rates of 90 and 30 to 40 percent, respectively. This response rate is similar to that observed with dasatinib. Approximately 15 percent of patients will discontinue nilotinib due to toxicities [31]. The dose approved by the US Food and Drug Administration is 400 mg twice daily in the setting of imatinib failure and 300 mg twice daily for previously untreated disease. Information on side effects and their management is discussed separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Nilotinib'.)

The following are the largest studies that have evaluated nilotinib in this setting:

- A phase 2 study examined the use of nilotinib in 321 patients with chronic phase CML and imatinib resistance (70 percent) or intolerance [32-34]. Patients received nilotinib 400 mg twice daily with escalation to 600 mg twice daily for inadequate response. Results included:
 - A major cytogenetic response, complete cytogenetic response, and major molecular response were attained in 59, 44, and 28 percent of patients, respectively. Response rates were similar in patients with imatinib resistance or intolerance.
 - Grade 3/4 side effects included thrombocytopenia (28 percent), neutropenia (28 percent), elevated lipase (15 percent), hyperglycemia (11 percent), hypophosphatemia

(10 percent), and QT prolongation (3 percent). Pleural effusion, pericardial effusion, or pulmonary edema occurred in <1 percent of patients.

- Estimated rates of overall and progression-free survival at two-years were 87 and 64 percent, respectively [33]. Corresponding rates at four years were 78 and 57 percent, respectively [34]. Responses appeared to be durable with 89 percent of those patients who achieved a complete cytogenetic response by 12 months maintaining it at four years.
- In an international open-label expanded access trial, 1422 patients with chronic phase CML and imatinib resistance (60 percent) or intolerance were treated with nilotinib 400 mg twice daily [35]. A major cytogenetic response was achieved in 45 percent (34 percent complete). Progression-free survival at 18 months was 80 percent. Severe (grade 3/4) toxicities included thrombocytopenia (22 percent), neutropenia (14 percent), elevated lipase (7 percent), hyperbilirubinemia (4 percent). Nonhematologic toxicities were generally mild, but included rash, headache, fatigue, pruritus, nausea, and myalgia.
- In another trial (ENESTcmr), 207 patients in complete cytogenetic response with detectable *BCR::ABL1* after at least two years of imatinib were randomly assigned to continue imatinib or switch to nilotinib [36]. A switch to nilotinib was associated with higher rates of undetectable *BCR::ABL1* at one year (13 versus 6 percent) and two years (22 versus 9 percent). Complete cytogenetic response was maintained in all patients treated with nilotinib, while three patients assigned to imatinib lost complete cytogenetic response. No patients had progressed to accelerated phase or blast crisis. Patients assigned to nilotinib were more likely to report severe (grade 3/4) adverse events (49 versus 22 percent) and less likely to remain on the assigned treatment (77 versus 91 percent). Adverse events were similar to those reported in other studies.

With follow-up of at least five years, the rate of 4.5 log molecular response (*BCR::ABL1* ≤ 0.0032 percent on the International Scale) was higher with nilotinib (twice daily doses of either 300 mg or 400 mg) compared with imatinib (54 and 52 versus 31 percent) [37]. However, patients treated with nilotinib had higher rates of cardiovascular events (CVE), including ischemic heart disease, ischemic cerebrovascular events, and peripheral artery disease. The rates of total CVEs were 7.5, 13.4, and 2.1 percent for nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib, respectively; this suggests that CVEs associated with nilotinib may be dose-dependent.

These trials support the use of nilotinib for the treatment of patients with CML in chronic phase after the failure of imatinib therapy. Nilotinib can also be incorporated into the treatment plan

of such patients who are candidates for HCT. (See 'Patients eligible for HCT' below.)

Cytogenetic and molecular response appears to correlate with survival. As an example, in the phase II study described above, estimated survival rates at 48 months were 95, 82, and 73 percent for patients with *BCR::ABL1* transcript levels ≤1 percent, 1 to 10 percent, and >10 percent, respectively [34]. Activity of nilotinib in patients with the highly resistant T315I, Y253H, and E255V/K mutations is limited [38-40]. The use of nilotinib in previously untreated disease and the relationship between cytogenetic response and survival are discussed elsewhere. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Nilotinib'.)

Bosutinib — Bosutinib is a dual kinase inhibitor that targets both the ABL and SRC pathways, but does not target KIT or PDGFR [41]. Uncontrolled prospective trials have evaluated the use of bosutinib in patients in chronic phase with resistance or intolerance to prior therapy. Bosutinib results in complete hematologic and cytogenetic response rates of approximately 85 and 40 percent, respectively. Although the follow-up of patients receiving bosutinib is shorter than for patients in trials of dasatinib and nilotinib, this response rate is similar to those observed with dasatinib and nilotinib. Bosutinib is approved by the US Food and Drug Administration for the treatment of chronic phase CML in adults with resistance or intolerance to prior therapy [42]. The recommended dose and schedule is 500 mg orally once daily with food.

A phase 1/2 trial of bosutinib (500 mg once daily) in 288 patients with CML with imatinib resistance (69 percent) or intolerance reported major cytogenetic responses in 31 percent of patients by 24 weeks [43]. After a median follow-up of 24 months, rates of complete hematologic remission, major cytogenetic response, and complete cytogenetic response were 86, 53, and 41 percent, respectively. Of the patients achieving a complete cytogenetic response, 64 percent attained a major molecular response. Estimates of progression-free and overall survival at two years were 81 and 91 percent, respectively [44]. The most common severe toxicities included diarrhea, rash, and vomiting.

Similar toxicities were noted when this study population was expanded to include a total of 570 patients [45]. When all grades of toxicity were considered, the most common nonhematologic toxicities were diarrhea (86 percent), nausea (46 percent), and vomiting (37 percent). These side effects were most common early after initiation of treatment and tended to decrease in severity over time. Severe (grade 3/4) hematologic toxicities were not uncommon: thrombocytopenia (30 percent), anemia (14 percent), and neutropenia (14 percent). Other laboratory abnormalities included hypermagnesemia, increased ALT, hypophosphatemia, increased lipase, hyperglycemia, and hyponatremia. Pleural effusions (10 percent), cardiac events (18 percent) and vascular events (13 percent) were observed. Most toxicity could be managed with concomitant medications, dose interruption, and/or dose reduction.

This study and the expansion cohort demonstrate that approximately 40 percent of patients with resistance or intolerance to imatinib will attain a complete cytogenetic response after treatment with bosutinib. Response rates are lower among patients who have previously received two tyrosine kinase inhibitors. Bosutinib is not active against the T315I mutation.

Bosutinib has also been studied in patients with newly diagnosed CML in chronic phase and in patients with accelerated phase or blast crisis. (See "Initial treatment of chronic myeloid leukemia in chronic phase", section on 'Bosutinib' and "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Bosutinib'.)

Ponatinib — Ponatinib is an orally administered BCR::ABL1 inhibitor that has demonstrated activity against the native and mutated BCR::ABL1 proteins and is the only TKI that is effective against the *BCR::ABL1* T315I mutation. Ponatinib is indicated for the treatment of adults with *BCR::ABL1* T315I-positive CML and for adults with CML for whom no other tyrosine kinase inhibitor is indicated.

Approval of ponatinib by the US Food and Drug Administration (FDA) and European Medicines Agency was accompanied by a boxed warning alerting patients and clinicians to the significant risk of arterial thrombosis and liver toxicity. Vascular complications, including arterial and venous thromboses and embolic events, occur in ≥27 percent of patients [46-48]. Because of the high risk of complications, a risk evaluation and mitigation strategy (REMS) has been put in place [48].

The recommended dose and schedule initially approved by the FDA was 45 mg orally once daily with or without food [49]. It is not known whether the thrombotic complications are dose related and if decreasing the dose of ponatinib will decrease the risk. In addition, it is not known if a dose reduction will compromise response. Despite this, it has been recommended that patients be treated with the lowest dose that is effective in that individual with close monitoring for disease progression. Additional studies are needed to determine whether lower doses are both effective and safer. Although there are no prospective data, many clinicians are recommending that patients continuing on ponatinib also receive aspirin.

The phase 2 PACE study of ponatinib reported major cytogenetic responses in 56 percent of the 203 patients with chronic phase CML resistant or intolerant to dasatinib or nilotinib and in 72 percent of the 64 patients in chronic phase with *BCR::ABL1* T315I mutations [50,51]. The median time to major cytogenetic response was 2.8 months and 82 percent were sustained at five years; estimated five-year overall survival was 73 percent. The initial dose of ponatinib was 45 mg daily, but was reduced to 30 or 15 mg daily in response to adverse events, and later in the

study was reduced prospectively for all patients. No specific mutations appeared to confer resistance.

The most common toxicities (all grades) reported in PACE II were rash (47 percent), abdominal pain (46 percent), thrombocytopenia (46 percent), headache (43 percent), dry skin (42 percent), and constipation (41 percent), most of which occurred within three months of treatment initiation [50,51]. With five year follow up, arterial obstructive events (AOE; ie, cardiovascular, cerebrovascular, and peripheral vascular events) were reported in 31 percent of patients with CML with the cumulative incidence of AOE^s increasing over time. Three patients died with AOE^s.

There are no prospective trials that have compared outcomes of patients with CML with the *BCR::ABL1* T315I mutation who were treated with ponatinib versus allogeneic HCT. In a retrospective analysis comparing these treatment approaches in this population, ponatinib resulted in better overall survival at 24 months (84 versus 61 percent, respectively) and 48 months (73 versus 56 percent, respectively) [52].

Further study with longer follow-up is necessary to better understand the toxicities associated with ponatinib. Initial trials reported serious arterial thromboses in approximately 8 percent of patients. However, the FDA reports that with further follow-up of multiple clinical trials using ponatinib, blood clots or narrowing of blood vessels were noted in at least 27 percent of patients, occurring as early as two weeks after starting ponatinib and in some patients without apparent cardiovascular risk factors [46,47]. As a consequence, the phase III "EPIC" trial comparing imatinib versus ponatinib in previously untreated patients with CML was terminated due to toxicity concerns [53].

The mechanism by which ponatinib interacts with the endothelium and pre-existing arteriosclerotic plaques is not known. Patients taking ponatinib should seek immediate medical attention if they experience symptoms suggesting a heart attack (such as chest pain or pressure; pain in their arms, back, neck, or jaw; or shortness of breath) or symptoms of a stroke (such as numbness or weakness on one side of the body; trouble talking; severe headache; or dizziness). Clinicians should be cautious about using ponatinib in patients with known atherosclerotic disease and hypertension. Those taking ponatinib should be monitored for the development of hypertension to allow for early medical intervention. Further details regarding toxicities and dose adjustments are available in the package insert [48].

Increased dose imatinib — Prior to the development of second generation TKIs, it was common to increase the dose of imatinib from 400 mg to 600 mg or 800 mg daily in patients who showed a decrease in response but were still able to tolerate imatinib. This approach was

supported by data showing that low trough plasma levels of imatinib can be seen in some patients with primary resistance [12,13,54]. Higher doses of imatinib may improve response by:

- Raising trough levels
- Controlling increased levels of *BCR::ABL1* produced by genomic amplification
- Inhibiting *BCR::ABL1* mutations with low orders of resistance to imatinib

A non-randomized study evaluated the use of increased dose imatinib in 84 patients with CML in chronic phase who had hematologic (21 patients) or cytogenetic (63 patients) failure of standard-dose imatinib [55]. At a median follow-up of five years from dose escalation, 40 percent had achieved a complete cytogenetic response. In a subset analysis, a complete cytogenetic response had been achieved by 52 and 5 percent of patients who had cytogenetic and hematologic failures, respectively. Once a major cytogenetic response was attained, 88 percent of patients sustained their response beyond two years.

A phase 2 study of 150 patients with imatinib-resistant CML in chronic phase randomized to treatment with dasatinib or increased dose imatinib reported that dasatinib (140 mg/day) resulted in a significantly higher percentage of complete hematologic responses (93 versus 82 percent), major cytogenetic responses (40 versus 16 percent), and major molecular responses (16 versus 4 percent) [24,56]. The benefit of dasatinib was most apparent when compared with the subgroup of patients whose imatinib dose was increased from 600 to 800 mg/day. The results were less striking in patients whose initial imatinib dose was 400 mg/day. When compared with those who received increased dose imatinib, patients treated with dasatinib were more likely to have maintained a major cytogenetic response at 18 months (90 versus 74 percent) [56].

We generally prefer a second generation TKI rather than increased dose imatinib, particularly in patients whose disease was resistant to 600 mg/day. This is principally based upon the results of the randomized phase II trial described above showing superior response rates with dasatinib compared with increased dose imatinib. A trial of dose increase to 800 mg is still reasonable in some patients with close monitoring for response and a switch to a new TKI if complete cytogenetic response is not reached.

PATIENTS ELIGIBLE FOR HCT

Therapeutic options — Eligibility criteria for allogeneic hematopoietic cell transplantation (HCT) vary by institution and are discussed above. There are two main therapy options for the

patient who has become intolerant of or resistant to tyrosine kinase inhibitors (TKI) and is eligible for HCT:

- Continuation of a second generation TKI
- Allogeneic HCT

There are limited data to guide the choice between these options. Continuation of a TKI or HCT are acceptable alternatives and a decision should be made after a detailed discussion with the patient. An overview of the trials, clinical outcomes, and experience with second generation TKIs and increased doses of imatinib are discussed above. A randomized phase II trial showed superior response rates with dasatinib compared with increased dose imatinib [24,56]. (See 'Initial management' above.)

Scoring systems have been devised in an attempt to predict the response of CML to a second generation TKI. As an example, analysis of 123 patients with chronic-phase CML intolerant or resistant to imatinib who underwent treatment with a second generation TKI identified two risk factors for progression [57]: the lack of a cytogenetic response to initial imatinib and an Eastern Cooperative Oncology Group performance status of 1 or more. Patients with zero, one, or two of these factors had rates of event-free survival at two years of 78, 49, and 20 percent, respectively. Another scoring system incorporated information on the best cytogenetic response to imatinib, the occurrence of neutropenia, and the Sokal score at diagnosis [58]. Other factors that might affect the response to a second generation TKI include adherence to imatinib therapy and point mutations in *BCR::ABL1* [9,22]. Validation of these scoring systems in independent patient cohorts is necessary before they can be widely applied with confidence. In practice, because the responses to second generation TKIs occur usually rapidly, we recommend repeating PCR evaluations about two months after switching; one should have concern if improvements are not apparent.

HCT is an appealing option for some patients since it is the only proven curative treatment option in CML. Among patients with certain clinical characteristics, five-year survival can be as high as 80 percent. However, early mortality is in the 10 to 20 percent range. Details on the efficacy and risks associated with HCT are presented separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)

Survival with HCT can be predicted with reasonable accuracy using a scoring system devised by the European Group for Blood and Marrow Transplantation (EBMT) (table 4) [59]. This scoring system incorporates the patient's age, stage of disease, time from diagnosis, and the closeness of the donor match. An ideal candidate for transplant would be a young (<40 years old) patient in chronic phase with an HLA identical sibling donor. The five-year overall survival rates for such

patients (EBMT score 0-2) ranged at the time of this scoring system's creation from 60 to 80 percent. However, with the advent of newer approaches to HCT, current overall survival rates are likely to be higher. (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)

The benefits, risks, and side effects of HCT and tyrosine kinase inhibitors should be discussed with the patient in some detail before a treatment decision is made. The main factors when deciding among these options are the patient's age, availability of an appropriate donor, and the patient's interest in undergoing HCT.

The most commonly used approach in patients without a *BCR::ABL1* mutation is to initiate therapy with either dasatinib, nilotinib, or bosutinib rather than initially performing HCT. Further therapy is dependent upon the cytogenetic response:

- Among those **without** a complete cytogenetic response (CCyR), we suggest HCT given the likelihood of disease progression without transplantation. However, we often treat with a third TKI if resistance is due to an acquired *ABL1* kinase domain mutation that has high sensitivity to a particular TKI (figure 1). As an example, if a TKI has an inhibitory concentration (IC_{50}) in the range of 50 nM or lower to the mutation, we treat with that TKI prior to proceeding to HCT.
- Among those **with** a CCyR, options include continued TKI therapy or HCT. Some clinicians prefer HCT immediately in such individuals, primarily due to concerns regarding the durability of these responses, although most suggest close monitoring with HCT offered should there be evidence of disease progression or cytogenetic relapse. Maturing data regarding second generation TKIs suggest that the responses will be durable in the vast majority of patients [60,61]. Patient age, the availability of sibling versus unrelated donor and other medical factors also influence the recommendation in individual patients.

T315I mutation — For patients with *BCR::ABL1* T315I, we consider treatment with asciminib or ponatinib acceptable.

Ponatinib and asciminib are the only TKIs with significant activity against the *BCR::ABL1* T315I mutation; treatment with dasatinib, nilotinib, or bosutinib is **not** an option for patients with the T315I mutation, since this mutation is associated with resistance to those agents. There are only limited long-term follow-up data with these agents, and the role of allogeneic HCT for patients who achieve a robust response to these TKIs is uncertain. In this setting, we simultaneously begin treatment with asciminib or ponatinib and initiate evaluation for allogeneic HCT, with plans to proceed with HCT upon evidence of progression or intolerance in eligible patients. Omacetaxine has also been approved for treatment of patients with the T315I mutation, although the follow-up duration in responders is short and it is unlikely that these

responses will be sustained indefinitely. (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Mutation-guided'.)

While there is a paucity of data on HCT in this setting, outcomes appear to be primarily dependent upon the disease phase at the time of HCT and comorbidities [62]. In an international retrospective analysis of 64 patients with *BCR::ABL1* T315I mutation who underwent allogeneic HCT, the 33 patients who were in chronic phase at the time of transplant had a treatment related mortality rate of 9 and 18 percent at 3 and 12 months post HCT, respectively [63]. At a median follow-up from HCT of 26 months, the median overall survival had not been reached for patients in CR at the time of HCT, indicating that patients with this TKI resistant mutation can be transplanted successfully.

There are no prospective trials that have directly compared outcomes of patients with CML and the *BCR::ABL1* T315I mutation treated with ponatinib versus allogeneic HCT. However, a retrospective, international, open label study reported that, compared with allogeneic HCT, treatment with ponatinib resulted in better overall survival [52]. (See 'Ponatinib' above.)

MONITORING DISEASE STATUS

The definition of degrees of response and a recommended schedule for monitoring disease status is discussed in detail separately (table 5 and table 1). Criteria have been suggested specifically for patients treated with second generation tyrosine kinase inhibitors (table 6) [4,31,58,64,65]. (See "Overview of the treatment of chronic myeloid leukemia".)

FAILURE TO RESPOND TO ≥2 TKIS

For patients who failed to respond adequately or were intolerant of ≥2 tyrosine kinase inhibitors (TKIs), we suggest asciminib, rather than treatment with a third TKI, omacetaxine, or allogeneic hematopoietic cell transplantation (HCT). This suggestion is based on a phase 3 trial that reported asciminib was well-tolerated and achieved a superior molecular response compared with bosutinib [66]; asciminib has not been directly compared with omacetaxine or with allogeneic HCT, which offers the potential to cure CP CML, but is considerably more toxic.

There are very limited data regarding long-term survival in this setting, except for ponatinib and bosutinib. In practice, we evaluate eligible patients for allogeneic HCT and follow their response to treatment very closely as described above. Patients not eligible for HCT are considered for treatment with another TKI, treatment with omacetaxine, or enrollment in a clinical trial. (See 'Patients eligible for HCT' above.)

With the exception of trials evaluating ponatinib and bosutinib, there is a paucity of data regarding the management of patients in chronic phase for whom both imatinib and a second generation TKI have failed to respond adequately; in particular, long term follow-up data are sparse. In practice, we evaluate eligible patients for allogeneic HCT and follow their response to treatment very closely as described above. Patients not eligible for HCT are considered for treatment with another TKI, treatment with omacetaxine, or enrollment in a clinical trial. (See 'Patients eligible for HCT' above.)

Asciminib — Asciminib is an allosteric inhibitor of BCR::ABL1 with a mechanism of action that is distinct from other TKIs; rather than binding to the ATP binding site, asciminib binds to a myristoyl site of BCR::ABL1, which locks the protein in an inactive conformation. Asciminib targets wild-type and mutant BCR::ABL1, including the T315I mutant.

- The multicenter phase 3 ASCEMBL trial reported that asciminib had superior efficacy compared with bosutinib for patients with chronic phase CML who were previously treated with ≥ 2 TKIs [66]. Patients were randomly assigned (2:1) to receive asciminib (40 mg twice daily by mouth) versus bosutinib (500 mg one daily by mouth). Major molecular response (MMR) rate at 24 weeks was 26 percent with asciminib and 13 percent with bosutinib. Asciminib was associated with fewer grade ≥ 3 adverse events (AEs; 51 versus 61 percent, respectively) and fewer AEs leading to treatment discontinuation (6 versus 21 percent).
- In a phase 1 study, asciminib was active and well-tolerated in 141 heavily pretreated patients with chronic phase CML who were resistant or intolerant of ≥ 2 prior ATP-competitive TKIs [67]. Among patients with a hematologic relapse, asciminib achieved complete hematologic response in 92 percent; complete cytogenetic response was achieved in 54 percent of patients without a prior complete cytogenetic response; and a major molecular response at 12 months was achieved in 48 percent of evaluable patients. Among patients with a T315I mutation at baseline, 28 percent achieved major molecular response by 12 months, including patients for whom ponatinib had failed. Dose-limiting adverse effects included asymptomatic elevations of serum lipase and clinical pancreatitis, and common adverse events included fatigue, headache, arthralgia, hypertension, and thrombocytopenia.

Asciminib is approved by the US Food and Drug Administration (FDA) for treatment of CP CML after ≥ 2 TKIs and for CML in CP with the *BCR::ABL1* T315I mutation.

Other TKIs — Nonrandomized single-arm trials have investigated the use of a third TKI in patients who have an inadequate response to trials of more than one TKI.

- A single institution observational study reported the outcomes of 48 patients with CML who failed therapy with imatinib and subsequently failed therapy with either dasatinib or nilotinib and were then treated with a third TKI (dasatinib or nilotinib) [68]. The following data were reported on the 25 patients in chronic phase at the time the third TKI was initiated:
 - Responses were seen including major molecular response (5 patients), complete cytogenetic response (3 patients), partial cytogenetic response (2 patients), minor cytogenetic response (3 patients), and complete hematologic response (6 patients) (table 1); six patients had no response.
 - The time to treatment failure, including discontinuation due to toxicity, was 20 months. After a median follow-up of 16 months, only 10 of the 25 chronic phase patients remained on third line therapy and some of these had worsening of their disease compared with their best response.
 - There was no clear difference between patients treated with either potential sequence of TKIs (ie, imatinib, dasatinib, nilotinib or imatinib, nilotinib, dasatinib).
- An international phase 2 study investigated the use of nilotinib in patients with CML in chronic phase (39 patients) or accelerated phase (21 patients) after the failure of both imatinib and dasatinib [69]. Among patients in chronic phase, 67 percent had discontinued dasatinib due to toxicity. After nilotinib initiation, 43 percent of patients in chronic phase had attained a major cytogenetic response (24 percent complete). At a median follow-up of 12 months, estimated rates of progression-free and overall survival at 18 months for patients in chronic phase were 59 and 86 percent, respectively. These are overall response rates and it is not clear what the response rate is in patients who were previously refractory to treatment with dasatinib.
- The phase 1/2 study of bosutinib in patients with failure of initial therapy included a subset analysis of the 118 patients who had been initially treated with imatinib followed by dasatinib and/or nilotinib prior to treatment with bosutinib [70]. A major cytogenetic response was seen in 32 percent (24 percent complete). After a median follow-up of 28.5 months, estimated two-year rates of progression-free and overall survival were 73 and 83 percent, respectively.

Thus, improvements are needed in the management of patients progressing on therapy with nilotinib or dasatinib, and the decision to use an alternative TKI as third-line therapy should take the *BCR::ABL1* mutational pattern into consideration.

Omacetaxine — Omacetaxine mepesuccinate (previously known as homoharringtonine) is a protein synthesis inhibitor that has demonstrated activity in patients with CML in chronic phase with a *BCR::ABL1* T315I mutation. Omacetaxine is approved by the US Food and Drug Administration for the treatment of chronic phase CML in adults with resistance or intolerance to two or more TKIs [71]. The recommended dose and schedule is 1.25 mg/m² subcutaneous injection twice daily for 14 days of a 28-day cycle for the induction phase and 1.25 mg/m² subcutaneous injection twice daily for 7 days of a 28-day cycle for maintenance.

A phase 2 study investigated the use of omacetaxine in 62 patients with chronic phase CML resistant to an initial TKI who had an identified *BCR::ABL1* T315I mutation [72]. Subcutaneous omacetaxine (1.25 mg/m²) was administered twice daily on days 1 through 14 of a 28-day cycle until hematologic response or a maximum of six cycles. Patients who achieved a hematologic response were then treated twice daily on days 1 through 7 of a 28-day cycle as maintenance. Rates of complete hematologic, major cytogenetic, and complete cytogenetic response were 77, 23, and 16 percent, respectively. Most responses were seen after the first cycle. Median progression-free survival was 7.7 months. Hematologic toxicity was common with severe (grade 3/4) thrombocytopenia, neutropenia, and anemia occurring in 76, 44, and 39 percent, respectively. Common nonhematologic toxicities included infection, diarrhea, nausea, pyrexia, fatigue, asthenia, and arthralgia.

In a second phase 2 study, 76 patients with chronic phase CML resistant to or intolerant of two or more TKIs were treated with subcutaneous omacetaxine at the same dose as schedule as described above [73,74]. Rates of complete hematologic, major cytogenetic, and complete cytogenetic response were 70, 18, and 9 percent, respectively. The median response duration was eleven months. Reported toxicities were similar to those described above.

The use of omacetaxine in patients with accelerated phase disease is discussed separately. (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Other treatments'.)

CLINICAL TRIALS

Often there is no better therapy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Additional information and instructions for referring a patient to an appropriate research center can be obtained from the United States National Institutes of Health (www.clinicaltrials.gov).

SPECIAL CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has increased the complexity of cancer care. Important issues include balancing the risk from treatment delay versus harm from COVID-19, ways to minimize negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited health care resources. These issues and recommendations for cancer care during the COVID-19 pandemic are discussed separately. (See "COVID-19: Considerations in patients with cancer".)

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 info" and the keyword(s) of interest.)

- 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)")

SUMMARY AND RECOMMENDATIONS

- Treatment with a BCR::ABL1 tyrosine kinase inhibitor (TKI) for chronic phase chronic myeloid leukemia (CML) should be discontinued for drug intolerance, a suboptimal response to initial therapy, or for relapse after an initial response to a TKI. (See 'Defining intolerance and resistance' above.)
- There is no universal definition of TKI intolerance. We consider a patient intolerant when a nonhematologic toxicity of grade 3 or 4 recurs despite appropriate dose reductions and optimal symptomatic management. Cytopenias are more often a sign of the drug's effectiveness, and less often due to drug toxicity. (See 'Defining intolerance and resistance' above.)
- All patients with presumed resistance should be questioned carefully to assure compliance with the recommended dose and avoidance of other medications or herbal supplements that may impair TKI efficacy. All patients with confirmed resistance should undergo mutation analysis of *BCR::ABL1* to help direct further therapy (figure 1). (See 'Resistance' above.)
- For most patients with intolerance to an initial TKI, we recommend treatment with another TKI rather than immediate allogeneic hematopoietic cell transplantation (HCT) (**Grade 1B**).

Response rates to a second-line TKI are generally lower in patients with primary treatment failure or following relapse compared with those patients who are intolerant of the initial TKI. For such patients, we suggest treatment with another TKI (**Grade 2B**). HCT is a reasonable alternative for young, fit patients with a matched donor. (See 'Therapeutic options' above.)

- For those patients who **lack** the *BCR::ABL1* T315I mutation, we recommend administration of a second generation TKI rather than increased doses of imatinib (**Grade 1B**).

Selection of a second generation TKI is based upon side effect profiles of these agents, knowledge of the individual's comorbid conditions, and occasionally by the presence of specific kinase mutations (table 3). We evaluate for possible allogeneic HCT while monitoring the response to therapy.

- Further management of these patients is guided by achievement of a complete cytogenetic response (CCyR):
 - Many patients who achieve a CCyR will obtain a long term response. For those who achieve a CCyR, we suggest continued TKI therapy with close monitoring (followed by HCT at the signs of relapse) rather than immediate HCT (**Grade 2B**). Patient age,

availability of an HLA-matched donor, and other medical factors may influence the recommendation in individual patients. (See 'Initial management' above and 'Therapeutic options' above.)

- For those patients who fail to achieve a CCyR and remain in chronic phase CML, we suggest evaluation for allogeneic HCT. However, if resistance is due to an acquired *ABL1* kinase domain mutation that has high sensitivity (eg, IC₅₀ in the range of 50 nM or lower) to a particular TKI (figure 1), we often treat with that TKI prior to proceeding to HCT. In patients without a mutation, a trial of a third-line TKI (**Grade 2C**) can be considered with close monitoring of response with referral for transplant should the response be inadequate.
- For those who fail to achieve a CCyR and are **not** HCT candidates, we offer a trial of another TKI. Other treatment options include the use of interferon alfa plus cytarabine, or monotherapy with hydroxyurea or busulfan. (See "Overview of the treatment of chronic myeloid leukemia".)
- The *BCR::ABL1* T315I mutation is resistant to most TKIs, except ponatinib and asciminib. For patients who harbor the *BCR::ABL1* T315I mutation, we suggest treatment with asciminib or ponatinib, rather than immediate HCT (**Grade 2B**). We simultaneously initiate evaluation for allogeneic HCT with plans to proceed with HCT upon evidence of progression or intolerance in eligible patients. (See 'Ponatinib' above and 'T315I mutation' above.)
- For patients who harbor the *BCR::ABL1* T315I mutation and are HCT-ineligible, we recommend the use of ponatinib initially rather than omacetaxine or a chemotherapeutic regimen (**Grade 1B**). Other options include the use of interferon alfa plus cytarabine, or monotherapy with hydroxyurea or busulfan. (See 'Initial management' above.)

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74. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. Cancer 2015; 121:1637.

Topic 4515 Version 61.0

GRAPHICS

Definitions of hematologic, cytogenetic, and molecular response in chronic myeloid leukemia^[1,2]

Response by type	Definitions
Hematologic	
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
Cytogenetic*	
Major	Complete: No Ph+ metaphases or $<1\%$ BCR::ABL1-positive nuclei of ≥ 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
Molecular[¶]	
MR ^{4.5}	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> (or other housekeeping genes) $\leq 0.0032\%$ (≥ 4.5 log reduction) on the international scale (IS)
	or
MR ⁴	Undetectable disease in cDNA with $\geq 32,000$ <i>ABL1</i> transcripts
	or
MR ³	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> $\leq 0.01\%$ (≥ 4 log reduction) on the IS
	or
MR ³	Undetectable disease in cDNA with $\geq 10,000$ <i>ABL1</i> transcripts
	or
MR ³	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> (or other housekeeping genes) $\leq 0.1\%$ (≥ 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 ≥ 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 ≥ 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.

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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Graphic 52082 Version 13.0

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.

Tyrosine kinase inhibitor activity on BCR-ABL1 mutations in chronic myeloid leukemia

	Imatinib (nM)	Nilotinib (nM)	Dasatinib (nM)
P-loop	Native BCR-ABL1	260	13
	M244V	2000	38
	G250E	1350	48
	Q252H	1325	70
	Y253H	>6400	450
	Y253F	3475	125
	E255K	5200	200
	E255V	>6400	430
	V299L	540	NA
	F311L	480	23
ATP binding site	T315I	>6400	>2000
	T315A	971	61
	F317L	1050	50
	F317V	350	NA
	M351T	880	15
	E355G	2300	NA
Catalytic domain	F359V	1825	175
	V379I	1630	51
	L387M	1000	49
	H396R	1750	41
	H396P	850	41
A-loop	High sensitivity		
	Intermediate sensitivity		
	High insensitivity		

Activity of imatinib mesylate and the second generation tyrosine kinase inhibitors nilotinib and dasatinib against a selection of BCR-ABL1 mutants found in patients with CML. All concentrations are shown in nanomoles per milliliter and represent IC₅₀ values.

CML: chronic myeloid leukemia; TKI: tyrosine kinase inhibitor; NA: not available.

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Graphic 109963 Version 4.0

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-	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.

Graphic 89930 Version 4.0

European Group for Blood and Marrow Transplantation risk assessment score for allogeneic transplantation in chronic myeloid leukemia

Item	Category	Score
Donor	HLA Identical sibling donor	0
	Matched unrelated donor	1
Stage	First chronic phase	0
	Accelerated phase	1
	Blast crisis or ≥2nd chronic phase	2
Age	<20 years	0
	20 to 40 years	1
	>40 years	2
Sex matching (donor/recipient)	All other matches	0
	Female donor, male recipient	1
Time to HCT from diagnosis	<12 months	0
	>12 months	1
Score	Treatment-related mortality (%)	5-year Overall Survival (%)
0	20	72
1	23	70
2	31	62
3	46	48
4	51	40
5	71	18
6	73	22
7	-	-

Scoring: Scoring is from zero to a maximum of seven, with points scored for each of the five risk categories, as shown in the upper table. Treatment-related mortality and five-year overall survivals as a function of the score are shown in the lower table. There were too few patients with a score of seven to adequately assess TRM and OS.

leukemia; HCT: hematopoietic cell transplantation; %: percent.

Data from: Gratwohl, A, et al. *Lancet* 1998; 352:1087.

Graphic 67260 Version 2.0

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.

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.

Definitions of the response to second-line therapy in chronic myeloid leukemia after failure of imatinib

	Optimal	Warning	Failure
Baseline	NA	No CHR or loss of CHR on imatinib or lack of CyR to first-line TKI or high risk	NA
Three months	BCR-ABL1 ≤10 percent and/or Ph+ <65 percent	BCR-ABL1 >10 percent and/or Ph+ 65 to 95 percent	No CHR or Ph+ >95 percent or new mutations
Six months	BCR-ABL1 ≤10 percent and/or Ph+ <35 percent	Ph+ 35 to 65 percent	BCR-ABL1 >10 percent and/or Ph+ >65 percent and/or new mutations
12 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 and/or new mutations
Then, and at any time	BCR-ABL1 ≤0.1 percent	CCA/Ph- (-7 or 7q-) or BCR-ABL1 >0.1 percent	Loss of CHR or loss of CCyR or PCyR New mutations Confirmed loss of MMR* CCA/Ph+

These definitions are mainly based on data reported for nilotinib and dasatinib, but can be used provisionally also for bosutinib and ponatinib, until more data are available. These definitions cannot apply to the evaluation of the response to third-line treatment.

NA: not applicable; CHR: complete hematologic response; CCyR: complete cytogenetic response; TKI: tyrosine kinase inhibitors; CCA/Ph-: clonal chromosome abnormalities in Ph- cells; PCyR: partial cytogenetic response; MMR: major molecular response, BCR-ABL1 ≥ 0.1 percent = MR^{3.0} or better; CCA/Ph+: clonal chromosome abnormalities in Ph+ cells.

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

Graphic 90421 Version 1.0

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