

Treatment of chronic myeloid leukemia in blast crisis

AUTHORS: Robert S Negrin, MD, Charles A Schiffer, MD

SECTION EDITOR: Richard A Larson, MD

DEPUTY EDITOR: Alan G Rosmarin, MD

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

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

This topic last updated: **Apr 20, 2020**.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder associated with the Philadelphia chromosome t(9;22)(q34;q11) and the *BCR-ABL1* fusion gene. This acquired genetic abnormality produces BCR-ABL1, a constitutively active tyrosine kinase that causes CML and is the target of tyrosine kinase inhibitors (TKI). CML is a triphasic disease, in which approximately 85 to 90 percent of patients present in a chronic stable phase and the remainder initially present in accelerated phase or blast crisis. Without treatment, chronic phase CML inevitably progresses to accelerated phase/blast crisis, but treatment with TKIs has dramatically reduced the rate of progression to blast crisis.

Treatment of CML in blast crisis is discussed here.

Related topics include:

- (See "Clinical manifestations and diagnosis of chronic myeloid leukemia".)
- (See "Overview of the treatment of chronic myeloid leukemia".)
- (See "Initial treatment of chronic myeloid leukemia in chronic phase".)
- (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy".)
- (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment".)
- (See "Hematopoietic cell transplantation in chronic myeloid leukemia".)
- (See "Molecular genetics of chronic myeloid leukemia".)

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".)

DEFINITION OF BLAST CRISIS

Blast crisis of CML is defined by the World Health Organization (WHO) by one of the following features [1]:

- ≥20 percent blasts in peripheral blood or bone marrow
- Extramedullary proliferation of blasts (ie, myeloid sarcoma)

Previously, some definitions of blast crisis used a threshold of ≥30 percent blasts in bone marrow, and this should be kept in mind when interpreting older studies. Nevertheless, patients in blast crisis have a poor prognosis regardless of the defining threshold [2,3].

Most cases of CML blast crisis are myeloid, but in 20 to 30 percent of cases the blasts are lymphoid [1].

EVALUATION UPON TRANSFORMATION

Patients with CML typically present in chronic phase and in the tyrosine kinase treatment era, and progression to blast crisis in patients who achieve and maintain a complete cytogenetic remission two years after diagnosis, is very rare. In contrast, before these drugs were available, the median time to progression was three to four years after diagnosis. Thus, most cases of blast crisis will have a known diagnosis of CML at the time of transformation. A minority of patients with CML will be in blast crisis at the time of diagnosis.

Transformation may be suggested clinically by the development of signs and symptoms more typical of acute leukemia (eg, night sweats, weight loss, fever, bone pain, symptoms of anemia and bleeding). Evaluation of the patient with suspected blast crisis includes the following:

- Laboratory studies include a complete blood count with differential, chemistries with liver and renal function and electrolytes, and glucose.
 - Unilateral bone marrow aspiration and biopsy should be sent for pathology review, flow cytometry, cytochemistry, and cytogenetics. Flow cytometry and cytochemistry are performed to classify the blasts as myeloid or lymphoid and cytogenetics evaluates for clonal evolution.
 - *BCR-ABL1* mutation analysis to aid in selection of a tyrosine kinase inhibitor (TKI).
 - Human leukocyte antigen (HLA) typing should be performed for patients who are candidates for allogeneic hematopoietic cell transplantation (HCT), and referral to a transplant center and a donor search should be initiated as soon as possible to minimize administrative delays should transplantation be indicated. (See "Determining eligibility for allogeneic hematopoietic cell transplantation".)
-

REMISSION INDUCTION

Goal of therapy — The goal of initial management of CML blast crisis is to revert to chronic phase, with plans to proceed with allogeneic hematopoietic cell transplantation (HCT) in chronic phase, if possible.

Treatment to revert blast crisis to chronic phase CML differs depending on the lineage of the blasts (ie, myeloid versus lymphoid), as described in the sections below.

Lymphoid blast crisis — Lymphoid blast crisis with a B lineage immunophenotype (ie, acute lymphoblastic leukemia [ALL]) accounts for approximately 30 percent of CML blast crisis [1]. Lymphoid blast crisis often responds to treatments used for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

Most cases of lymphoid blast crisis develop in patients who are currently being treated with a tyrosine kinase inhibitor (TKI) or were previously treated with a TKI. For such patients, a switch to a second or third generation TKI is necessary. A TKI can be administered alone or in combination with lower intensity chemotherapy. Choice of TKI and chemotherapy are discussed separately. (See "Induction therapy for Philadelphia chromosome positive acute lymphoblastic leukemia in adults", section on 'TKI plus chemotherapy'.)

For the rare patient who has not been treated with a TKI, therapy should be given as described for "de novo" Ph+ ALL. (See "Induction therapy for Philadelphia chromosome positive acute lymphoblastic leukemia in adults".)

Retrospective studies have reported on the outcomes of patients with lymphoid blast crisis treated with regimens for Ph+ ALL. In one single institution study, 42 patients with lymphoid blast phase CML were treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (Hyper-CVAD) alternating with high-dose methotrexate and cytarabine plus either imatinib (27 patients) or dasatinib (15 patients) [4]. The majority (90 percent) achieved a complete hematologic response, with complete cytogenetic remission and complete molecular remission occurring in 58 and 25 percent, respectively. Median duration of remission was 14 months, and median overall survival was 17 months. Allogeneic HCT was associated with longer median survival (93 versus 9 months).

Myeloid blast crisis — Myeloid blast crisis (ie, acute myeloid leukemia [AML]) accounts for approximately 70 percent of CML blast crisis [1].

The preferred initial treatment is the use of a TKI (with or without chemotherapy) followed by an allogeneic HCT for eligible patients. The decision to incorporate AML-type induction chemotherapy into the treatment regimen depends upon whether the patient presents de novo or evolves to blast crisis while on a TKI. Although we treat de novo myeloid blast crisis with TKI alone until we can assess the response, if myeloid blast crisis develops while a patient is already taking a TKI, we administer AML-type induction chemotherapy combined with a more potent TKI for remission induction. (See "Acute myeloid leukemia: Induction therapy in medically-fit adults".)

Survival after allogeneic HCT correlates with disease phase at the time of transplantation with estimated two-year survival rates of 25, 50, and 65 percent for those in blast crisis, accelerated phase, and chronic phase, respectively [5]. A reasonable plan is an attempt to return the patient to an earlier phase of disease, with suitable candidates subsequently undergoing allogeneic HCT [6]. TKI treatment prior to transplantation has not been associated with an increase in transplant-associated morbidity or mortality [7]. (See "Hematopoietic cell transplantation in chronic myeloid leukemia", section on 'Pretreatment with TKIs'.)

Choice of TKI — There is a paucity of data regarding the choice of TKI to be used as the initial therapy for patients with blast crisis, regardless of whether the patient is a candidate for HCT. In general, we suggest treatment with a second generation TKI (eg, dasatinib, nilotinib) rather than imatinib. Second generation TKIs should certainly be used if the disease progression/blast crisis occurred while the patient was already taking imatinib for earlier stage CML. Similarly, ponatinib can be considered if the progression occurred while the patients was receiving dasatinib, nilotinib, or bosutinib. This preference is largely based on the extrapolation of data from randomized trials of these agents as initial therapy in patients with chronic phase CML. In these trials, second generation TKIs resulted in faster and deeper responses than imatinib,

especially among patients with higher risk chronic phase CML [8-11]. Given the expected lower response rates in blast crisis, the greater potency of these agents would be expected to have an even more important role. In addition, second generation TKIs have been proven to induce responses in imatinib-resistant CML, and this resistance is more likely to occur in blast crisis.

A choice among agents should also take into consideration the drug side effect profiles, results from a *BCR-ABL1* kinase mutation analysis, and the patient's comorbidities (table 1). Dasatinib has the advantage of being able to cross the blood brain barrier. The following sections review data regarding their use in blast crisis. Randomized trials comparing these agents in chronic phase CML are presented separately.

Imatinib — Imatinib is approved in the United States for the treatment of adults in blast crisis. The approved dose in this setting is 600 mg by mouth daily. The following is a summary of trials that have investigated the use of imatinib in the treatment of CML in blast crisis. It should be noted that these trials were conducted in the "pre-imatinib" era and hence these patients had not previously been treated with a TKI:

- In a dose-escalating pilot study, patients with CML in blast crisis (defined in this study as >30 percent blasts in the peripheral blood or bone marrow) were treated with imatinib at doses ranging from 300 to 1000 mg/day [12]. On an intent-to-treat basis, the following results were reported:
 - Overall response rates were 55 and 70 percent in patients with myeloid and lymphoid blast crises, respectively. Complete hematologic responses were attained in 4 of 38 patients with myeloid blast crisis and 4 of 20 patients in lymphoid blast crisis. Major cytogenetic responses were observed in 7 of the 58 patients; five of the seven responses were complete.
 - Nine of the 21 responders with myeloid blast crisis and 12 of the 14 with lymphoid blast crisis relapsed, at median times of 84 and 58 days, respectively.
 - Imatinib was generally well-tolerated, with nausea, vomiting, and edema in 55, 41, and 41 percent, respectively. Grade 4 neutropenia and thrombocytopenia occurred in 40 and 33 percent, respectively. None of the 16 deaths in the study was thought to be related to treatment with this agent.
- An analysis of 260 patients with CML in blast crisis from three large phase II studies evaluated the use of imatinib 600 mg daily [13]. At 36 months after initiation of imatinib, an estimated 14 percent of patients were alive and only 7 percent were disease free.

- In subsequent studies, patients in blast crisis were treated with doses ranging from 300 to 1000 mg/day; objective and major cytogenetic responses were noted in 52 and 16 percent, respectively, and were not different between myeloid and lymphoid crises [14,15]. Median survivals were 3, 6, and 17 months for those with no response, unsustained response, or sustained response, respectively [14]. Thus, while imatinib can provide palliative benefit to many patients with blast crisis, the effects are usually transient.

Of particular note, imatinib has a limited ability to penetrate the intact blood/brain barrier [16,17], and thus may not be sufficient initial therapy for patients in blast crisis with central nervous system involvement [18-20].

Dasatinib — Dasatinib is approved in the United States for the treatment of adults in blast crisis with resistance or intolerance to prior therapy. The approved dose in this setting is 140 mg once daily.

A phase II, open-label, single-arm clinical trial examined the use of dasatinib 70 mg twice daily in patients with CML in myeloid (74 patients) or lymphoid (42 patients) blast crisis who were resistant to (105 patients) or intolerant of (11 patients) imatinib [21]. After eight months of follow-up, the following results were obtained:

- Complete hematologic responses were seen in 26 percent.
- Complete cytogenetic responses were seen in 27 and 43 percent of patients with myeloid and lymphoid blast crisis, respectively.
- Hematologic responses occurred rapidly with a median time to achieve response of one to two months.
- Dasatinib was well tolerated with discontinuation secondary to toxicity seen in only 11 and 2 percent of patients with myeloid and lymphoid blast crisis, respectively. However, dose interruptions were required by 64 percent and 33 percent of these patients, respectively.

Extension of this study to include 109 patients with myeloid and 48 patients with lymphoid blast phase CML reported median overall survival times of 11.8 and 5.3 months, respectively, with curves suggesting a continual rate of treatment failure with longer follow-up [22].

A phase III randomized trial evaluated the use of dasatinib 140 mg once daily versus dasatinib 70 mg twice daily in 210 patients with CML in blast phase who demonstrated resistance to (84 percent) or intolerance of imatinib therapy [23]. The two treatment doses had similar efficacy. Once daily dosing had a trend towards improved tolerability with fewer patients requiring dose reductions/interruptions.

- Of the 149 patients in myeloid blast phase, complete hematologic responses were seen in 26 patients (17 percent). Rates of major and complete cytogenetic response were 26 and 17 percent, respectively.
- Of the 61 patients in lymphoid blast phase, rates of complete hematologic, major cytogenetic, and complete cytogenetic response were 18, 43, and 34 percent, respectively.
- Dasatinib does not have activity against the highly resistant T315I mutation.

Since the two dosing schedules appear to have equal efficacy and there may be a decrease in toxicity in addition to the convenience of once daily dosing, the 140 mg once daily dosing schedule may be preferable. Side effects of dasatinib and their management are discussed separately. (See "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment", section on 'Dasatinib'.)

Nilotinib — Nilotinib is a second generation TKI that has been used off-label for the treatment of CML in blast crisis. There is a paucity of data in this setting. A prospective study evaluated the efficacy of nilotinib (400 mg twice daily) in patients with CML in blast crisis [24]. After a minimum follow-up of 24 months, the following were noted:

- In the 105 patients with myeloid blast phase, responses included major hematologic response (60 percent), major cytogenetic response (38 percent), and complete cytogenetic response (30 percent). Twelve patients underwent allogeneic HCT. Median duration of major cytogenetic response was 11 months and median overall survival was 10 months with estimated rates of survival at one and two years of 44 and 32 percent, respectively.
- In the 31 patients with lymphoid blast phase, responses included major hematologic response (59 percent), major cytogenetic response (52 percent), and complete cytogenetic response (32 percent). Two patients underwent HCT. Median duration of major cytogenetic response was three months, and median overall survival was eight months with estimated rates of survival at one and two years of 35 and 10 percent, respectively.
- Nilotinib does not have activity against the highly resistant T315I mutation.

Bosutinib — Bosutinib is approved in the United States for the treatment of adults in blast crisis with resistance or intolerance to prior therapy. The approved dose is 500 mg once daily.

Preliminary results are available for phase I/II study of bosutinib in 546 patients with CML with resistance or intolerance to at least one TKI that included 60 patients with blast crisis [25]. At a minimum follow-up of 12 months, 28 percent achieved a hematologic response (15 percent

complete hematologic response). The most common severe (grade 3/4) toxicities included diarrhea (9 percent), rash (9 percent), and vomiting (3 percent).

Bosutinib does not have activity against the highly resistant T315I mutation. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Bosutinib' and "Initial treatment of chronic myeloid leukemia in chronic phase", 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 available effective against the T315I mutation. Ponatinib received accelerated approval by the US Food and Drug Administration (FDA) for the treatment of CML in adults with resistance or intolerance to prior TKI therapy [26]. The phase II PACE trial of ponatinib reported major hematologic responses (MHR) in 31 percent of the 62 patients with blast crisis (myeloid or lymphoid) resistant or intolerant to dasatinib or nilotinib, including patients with T315I mutations [27]. Median time to MHR and median duration of MHR were four and five months, respectively. At 12 months, 42 percent had a sustained response. Major cytogenetic response and complete cytogenetic response were attained in 23 and 18 percent, respectively. Estimated progression-free and overall survival rates at one year were 55 and 84 percent, respectively.

Importantly, ponatinib has a boxed warning regarding the risk of vascular occlusion, heart failure, and liver toxicity and requires access through a risk evaluation and mitigation strategy (REMS) [28]. While the exact risk is unknown, prospective studies suggest that vascular complications, including arterial and venous thromboses and embolic events, occur in ≥27 percent of patients [28-30]. Ponatinib is indicated for the treatment of adults with T315I-positive CML and for adults with CML for whom no other TKI is indicated. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Ponatinib'.)

The recommended dose and schedule is 45 mg orally once daily with or without food. 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 in progress in patients in chronic phase 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.

In the PACE trial, the most common toxicities were rash (74 percent), thrombocytopenia (46 percent), and abdominal pain (46 percent), as reported in the form of an abstract; most occurred in the first year of treatment [31]. Cardiovascular, cerebrovascular, and peripheral

vascular events occurred in 7, 4, and 5 percent, respectively [27]. The majority of patients with vascular events had at least one vascular risk factor (eg, hypertension, diabetes, hypercholesterolemia, obesity). Of the patients who continued ponatinib after a vascular event, 36 percent had subsequent events. Overall, severe adverse events led to the discontinuation of therapy in 11 percent of patients. Five patients died, one death was thought to be related to ponatinib (gastric hemorrhage).

Data regarding the use of ponatinib in chronic phase or accelerated phase CML are presented separately. (See "Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy", section on 'Ponatinib' and "Accelerated phase chronic myeloid leukemia: Diagnosis and treatment".)

RESPONSE EVALUATION

It is important to monitor the patient's disease status at regular intervals in order to detect patients who do not respond optimally. A variety of monitoring schedules for patients with CML are acceptable. Patients in blast crisis need to be seen frequently for management of cytopenias and frequently require red blood cell and platelet transfusion. Post-transfusion platelet increments are often compromised by the splenomegaly that commonly accompanies blast crisis. Because cytogenetic response can sometimes occur in the absence of hematologic count recovery, it is reasonable to perform a bone marrow examination after approximately a month of treatment in patients who seem to have responded in terms of elimination of circulating blasts and palpable splenomegaly.

The European LeukemiaNet has developed definitions of treatment failure, optimal response, and warning signs following the use of a tyrosine kinase inhibitor (TKI) as first-line therapy (table 2) and the use of second-line therapy in cases of imatinib failure (table 3) [32,33]. The definitions of hematologic, cytogenetic, and molecular responses are discussed in detail separately (table 4). (See "Overview of the treatment of chronic myeloid leukemia".)

POST-REMISSION THERAPY

Assessing HCT eligibility — Allogeneic hematopoietic cell transplantation (HCT) offers the best opportunity for long-term survival following transformation to blast crisis. As such, all patients should be referred to a transplant center at the time of transformation for transplant eligibility. Eligibility for HCT varies across countries and institutions. Although data supporting such criteria are limited, patients are often excluded based on age (>70 years old), uncontrolled

infection, cardiac, pulmonary, liver or renal dysfunction, and/or psychosocial variables. General guidelines are presented separately. (See "Determining eligibility for allogeneic hematopoietic cell transplantation".)

Either matched-related, matched-unrelated donors, haploidentical related donors, or umbilical cord blood (the latter two sources preferable at times since donors can be identified rapidly) can be used for CML in the setting of blast crisis since other treatment options are not very effective. (See "Hematopoietic cell transplantation in chronic myeloid leukemia" and "Donor selection for hematopoietic cell transplantation".)

Eligible for HCT — For patients with CML in blast crisis who are candidates for allogeneic HCT, we recommend the use of a tyrosine kinase inhibitor (TKI) as initial therapy followed by HCT rather than immediate HCT. We suggest transplantation once a maximum response to a TKI has been realized rather than continuation of the TKI without HCT. The rationale for this approach is that success with HCT is most likely in patients with relatively quiescent disease. There are no data comparing continuation of a TKI versus transplantation in the relatively small group of patients in whom a complete cytogenetic response is obtained with TKI treatment. There is concern, however, that if HCT is postponed until a second TKI is required for relapse, the chance of inducing a similar level of response is lower.

Treatment with a TKI is given prior to HCT in an attempt to return the patient to an earlier phase of disease. Imatinib treatment for blast crisis can result in objective responses in approximately half of patients with 15 percent attaining a second chronic phase [15]. Responses appear to be higher for those treated with second generation TKIs. Because of the truly transient nature of responses in this phase of CML, treatment with imatinib alone should be considered palliative and is not an appropriate longer term treatment alternative for patients who are eligible for HCT.

It is uncertain whether there is any benefit to using a TKI after HCT for patients transplanted for chronic phase CML if a complete molecular remission has been achieved; however, we recommend a TKI if a reduced intensity regimen is utilized for the transplant. Frequent *BCR-ABL1* measurable residual disease (MRD) monitoring is advisable for such patients. For patients transplanted for CML in myeloid or lymphoid blast crisis, we suggest the use of a TKI for two years after allogeneic HCT, if tolerable, rather than postponing its use until the emergence of MRD positivity, especially if nonmyeloablative conditioning is used. It should be noted, however, that there are few data about whether longer use of a TKI is advisable.

Chemotherapy alone has been used for patients in blast crisis in an attempt to return the patient to an earlier phase of disease and then proceed with transplantation in eligible patients

[34]. The response rate in myeloid blast crisis is quite low and the addition of a TKI is generally recommended.

Ineligible for HCT — Patients with CML in blast crisis who are not candidates for allogeneic HCT have a very poor prognosis. Treatment options include the chronic administration of a TKI or enrollment in a clinical trial. The median survival of patients with blast crisis treated with imatinib therapy in several phase II trials were 3, 6, and 17 months for those with no response, unsustained response, or sustained response, respectively [14]. Among patients who show a response to treatment, we recommend continuing the TKI as long as the patient continues to show a response. Even though TKIs are not curative and responses are often short-lived, they are oral medications that are fairly well tolerated. In addition, very occasional patients may enjoy a long term response with TKIs alone [35].

Detailed information on drug toxicity and management of side effects is discussed separately. The risks of discontinuing treatment in responding patients are presented separately. (See "Initial treatment of chronic myeloid leukemia in chronic phase".)

Prior to the development of TKIs, patients with blast crisis were often treated with cytarabine-based regimens. Although there have been no randomized trials that have directly compared imatinib with such regimens, a historical comparison shows significantly better response rates (55 versus 29 percent) and median survival (7 versus 4 months) with less toxicity with imatinib compared with treatment with chemotherapy [15].

No trials have compared the use of a TKI alone possibly followed by chemotherapy after a response has been achieved (if a transplant is not feasible) with the combination of chemotherapy and a TKI given together as initial treatment. Given the poor results with chemotherapy alone, most, if not all, patients should receive a TKI as part of their initial induction regimen.

A small (<1 percent) number of patients with apparently de novo AML with no prior history or signs of CML will be found to have a t(9;22) chromosomal translocation when their cytogenetic results become available. Often, they have already received and sometimes completed standard AML induction therapy. It is reasonable to add a TKI when the diagnosis is established, although it might be expected that the duration of cytopenias may be more prolonged.

TREATMENT AFTER FAILURE OF INITIAL THERAPY

There is limited evidence to guide the treatment of patients with CML in blast crisis who fail to respond to initial therapy. Patients progressing despite treatment with one tyrosine kinase

inhibitor (TKI) might respond to another. Options include dasatinib, nilotinib, bosutinib, or ponatinib [24,36,37]. The choice is influenced by prior TKI exposure as well as the results of that treatment, *BCR-ABL1* mutational analysis [38,39], drug side effect profiles, and patient comorbidities (table 1). Importantly, ponatinib is the only available TKI with activity against the T315I mutation. The use of these agents are presented above. (See 'Choice of TKI' above.)

Options for treatment of relapse after allogeneic hematopoietic cell transplantation (HCT) include donor lymphocyte infusion and TKIs. This is discussed in more detail separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia", section on 'Monitoring MRD post-HCT'.)

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)")
-

SUMMARY AND RECOMMENDATIONS

As advances are made in the treatment of chronic phase chronic myeloid leukemia (CML), fewer patients (approximately 7 percent at five years) are progressing to accelerated phase and blast crisis. However, 10 to 15 percent of patients will initially present in accelerated phase or blast crisis, and it is likely that a larger fraction of patients will present in more advanced stages in less medically developed countries. Treatment of these more advanced phases of CML is difficult. In general, an attempt is made to return the patient to a chronic phase with plans to proceed to allogeneic hematopoietic cell transplantation (HCT) after an initial response.

- Blast crisis can occur de novo or can evolve slowly or rapidly during tyrosine kinase inhibitor (TKI) therapy of chronic phase CML. In either case, there is marked chemotherapy resistance, and responses to TKIs (with or without chemotherapy) tend to be short-lived.
- All patients with blast crisis should undergo *BCR-ABL1* kinase mutational analysis to aid in TKI selection. All patients should also be referred to a transplant center and evaluated promptly for allogeneic HCT, as only allogeneic HCT offers a chance at long-term survival. Candidates for HCT should have human leukocyte antigen (HLA) typing and a donor search should be initiated. (See 'Evaluation upon transformation' above.)
- Patients with CML in lymphoid blast crisis are treated with combination chemotherapy in addition to a BCR-ABL1 TKI. This is discussed in detail separately. (See "Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults", section on 'Philadelphia chromosome positive ALL'.)
- For patients with newly diagnosed CML in myeloid blast crisis who are eligible for HCT, we recommend initial treatment with a TKI rather than initial HCT (**Grade 1B**). For most patients, we suggest treatment with a second generation TKI (eg, nilotinib, dasatinib) rather than imatinib (**Grade 2C**). Imatinib may be considered for patients in whom second generation TKIs would be cost prohibitive. HCT should be performed once a maximal response to the TKI is realized. (See 'Eligible for HCT' above.)
- For patients with newly diagnosed CML in myeloid blast crisis who are ineligible for HCT, we suggest initial treatment with a TKI rather than the combination of a TKI plus chemotherapy (**Grade 2B**). Among patients who show a response to treatment, we recommend continuing the TKI as long as the patient continues to show a response (**Grade 1A**). Although we treat de novo myeloid blast crisis with TKI alone until we can assess the response, if myeloid blast crisis develops while a patient is already taking a TKI, we administer AML-type induction chemotherapy combined with a more potent TKI for remission induction. (See 'Ineligible for HCT' above.)

- For patients with CML in blast crisis who are intolerant of or resistant to an initial TKI, we recommend the administration of another TKI (**Grade 1B**). This regimen is used in an attempt to return the patient to a second chronic phase, with suitable candidates subsequently undergoing HCT. (See 'Treatment after failure of initial therapy' above.)
- Options for the treatment of relapse after allogeneic HCT include donor lymphocyte infusion and an alternative tyrosine kinase inhibitor. These options are discussed in detail separately. (See "Hematopoietic cell transplantation in chronic myeloid leukemia", section on 'Monitoring MRD post-HCT'.)

Use of UpToDate is subject to the Terms of Use.

REFERENCES

1. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition, Swerdlow SH, Campo E, Harris NL, et al. (Eds), International Agency for Research on Cancer (IARC), Lyon 2017.
2. Cortes JE, Talpaz M, O'Brien S, et al. Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. *Cancer* 2006; 106:1306.
3. Hehlmann R. How I treat CML blast crisis. *Blood* 2012; 120:737.
4. Strati P, Kantarjian H, Thomas D, et al. HCVAD plus imatinib or dasatinib in lymphoid blastic phase chronic myeloid leukemia. *Cancer* 2014; 120:373.
5. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood* 2014; 123:3664.
6. Lange T, Günther C, Köhler T, et al. High levels of BAX, low levels of MRP-1, and high platelets are independent predictors of response to imatinib in myeloid blast crisis of CML. *Blood* 2003; 101:2152.
7. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006; 108:1809.
8. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2010; 362:2260.
9. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; 362:2251.
10. Gurion R, Gafter-Gvili A, Vidal L, et al. Has the time for first-line treatment with second generation tyrosine kinase inhibitors in patients with chronic myelogenous leukemia

- already come? Systematic review and meta-analysis. *Haematologica* 2013; 98:95.
11. Jabbour E, Kantarjian HM, Saglio G, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 2014; 123:494.
 12. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001; 344:1038.
 13. Silver RT, Talpaz M, Sawyers CL, et al. Four years of follow-up of 1027 patients with late chronic phase, accelerated phase, or blast crisis chronic myeloid leukemia treated with imatinib in three large phase II trials (abstract). *Blood* 2004; 104:abstract 23.
 14. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002; 99:3530.
 15. Kantarjian HM, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. *Blood* 2002; 99:3547.
 16. Wolff NC, Richardson JA, Egorin M, Ilaria RL Jr. The CNS is a sanctuary for leukemic cells in mice receiving imatinib mesylate for Bcr/Abl-induced leukemia. *Blood* 2003; 101:5010.
 17. le Coutre P, Kreuzer KA, Pursche S, et al. Pharmacokinetics and cellular uptake of imatinib and its main metabolite CGP74588. *Cancer Chemother Pharmacol* 2004; 53:313.
 18. Bujassoum S, Rifkind J, Lipton JH. Isolated central nervous system relapse in lymphoid blast crisis chronic myeloid leukemia and acute lymphoblastic leukemia in patients on imatinib therapy. *Leuk Lymphoma* 2004; 45:401.
 19. Leis JF, Stepan DE, Curtin PT, et al. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). *Leuk Lymphoma* 2004; 45:695.
 20. Rytting ME, Wierda WG. Central nervous system relapse in two patients with chronic myelogenous leukemia in myeloid blastic phase on imatinib mesylate therapy. *Leuk Lymphoma* 2004; 45:1623.
 21. Cortes J, Rousselot P, Kim DW, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007; 109:3207.
 22. Cortes J, Kim DW, Raffoux E, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. *Leukemia* 2008; 22:2176.

23. Saglio G, Hochhaus A, Goh YT, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. *Cancer* 2010; 116:3852.
24. Giles FJ, Kantarjian HM, le Coutre PD, et al. Nilotinib is effective in imatinib-resistant or - intolerant patients with chronic myeloid leukemia in blastic phase. *Leukemia* 2012; 26:959.
25. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203341lbl.pdf (Accessed on September 05, 2012).
26. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf?et_cid=30657199&et_rid=463648356&linkid=http%3a%2f%2fwww.accessdata.fda.gov%2fdrugsatfda_docs%2flabel%2f2012%2f203469lbl.pdf (Accessed on December 17, 2012).
27. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013; 369:1.
28. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203469s007s008lbl.pdf (Accessed on January 22, 2014).
29. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm370971.htm> (Accessed on October 15, 2013).
30. <http://www.fda.gov/Drugs/DrugSafety/ucm379554.htm> (Accessed on January 14, 2014).
31. Kantarjian HM, Pinilla-Ibarz J, Le Coutre PD, et al. Five-year results of the ponatinib phase II PACE trial in heavily pretreated CP-CML patients (pts). [Abstract]. *J Clin Oncol* 2017; 35:7012.
32. 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.
33. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood* 2013; 122:872.
34. Axdorph U, Stenke L, Grimfors G, et al. Intensive chemotherapy in patients with chronic myelogenous leukaemia (CML) in accelerated or blastic phase--a report from the Swedish CML Group. *Br J Haematol* 2002; 118:1048.
35. Valent JN, Schiffer CA. Prevalence of large granular lymphocytosis in patients with chronic myelogenous leukemia (CML) treated with dasatinib. *Leuk Res* 2011; 35:e1.
36. Kantarjian HM, O'Brien S, Cortes JE, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. *Blood* 2002; 100:1590.
37. DeAngelo DJ, Hochberg EP, Alyea EP, et al. Extended follow-up of patients treated with imatinib mesylate (gleevec) for chronic myelogenous leukemia relapse after allogeneic

- transplantation: durable cytogenetic remission and conversion to complete donor chimerism without graft-versus-host disease. Clin Cancer Res 2004; 10:5065.
38. O'Hare T, Eide CA, Deininger MW. Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood 2007; 110:2242.
39. Soverini S, Hochhaus A, Nicolini FE, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood 2011; 118:1208.

Topic 4512 Version 21.0

GRAPHICS

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;	Active against <i>BCR::ABL1 T315I</i> mutation; limited long-term safety data

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

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.

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

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

Response by type	Definitions
Hematologic	
Complete	WBC <10 × 10 ⁹ /L
	Basophils <5%
	No myelocytes, promyelocytes, myeloblasts in the differential
	Platelet count <450 × 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) ≤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
	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> ≤0.01% (≥ 4 log reduction) on the IS
MR ³	or
	Undetectable disease in cDNA with $\geq 10,000$ <i>ABL1</i> transcripts
MR ³	Detectable disease with ratio of <i>BCR::ABL1</i> to <i>ABL1</i> (or other housekeeping genes) ≤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

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.
-

Graphic 52082 Version 13.0

→