



Blast Phase Chronic Myelogenous Leukemia

Benjamin Powers, MD; and Suman Kambhampati, MD

The dramatic improvement in survival with tyrosine kinase inhibitors has not been demonstrated in the advanced blast phase of chronic myelogenous leukemia where the goal is to revert the disease to a clinical remission and/or chronic phase long enough so that eligible patients may undergo allogeneic stem cell transplantation.

Chronic myelogenous leukemia (CML) is caused by the constitutively active BCR-ABL fusion protein that results from t(9;22), the Philadelphia (Ph⁺) chromosome. Chronic myelogenous leukemia typically evolves through 3 clinical phases: an indolent chronic phase, an accelerated phase, and a terminal blast phase analogous to acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). Fortunately, today more than 80% of patients are diagnosed in the chronic phase of the disease.¹

Before the development of the tyrosine kinase inhibitor (TKI) imatinib, >20% of the patients with chronic phase CML progressed to the blast phase every year.² Based on data from 8 years of follow-up with imatinib therapy, the rate of progression to the advanced phases of CML is about 1% per year, with freedom from progression at 92%.³ For the majority of patients with chronic phase CML, due to advances in treat-

ment, the disease does not affect mortality.

For those who progress to the terminal blast phase of CML, survival is typically measured in months unless allogeneic stem cell transplant (allo-SCT) is an option. This article will review one of the major remaining problems in CML: how to manage blast phase CML.

DEFINITION AND DIAGNOSIS

Defining blast phase CML can be confusing, because different criteria have been proposed, none of which are biologically based. The most widely used definition is set forth by the European LeukemiaNet, recommending 30% blasts in the blood or bone marrow or the presence of extramedullary disease.¹ Clinically, blast phase CML may present with constitutional symptoms, bone pain, or symptoms related to cytopenias (fatigue, dyspnea, bleeding, infections).

Diagnostic workup should include a complete blood cell count (CBC) with differential, bone marrow analysis with conventional cytogenetics, flow cytometry to determine whether the blast phase is of myeloid or lymphoid origin, and molecular mutational analysis of the BCR-ABL tyrosine kinase domain to

help guide the choice of TKI. If age and performance status are favorable, a donor search for allo-SCT should be started promptly.

Chronic myelogenous leukemia cells that contain the BCR-ABL kinase protein are genetically unstable.^{4,5} Additional cytogenetic aberrations (ACAs) are seen in up to 80% of those with blast phase CML and are the most consistent predictor of blast transformation in those with chronic phase CML.⁶ Chromosomal changes are broken down into the nonrandom, “major route” ACAs (trisomy 8, additional Ph⁺ chromosome, isochromosome 17q, trisomy 19), considered likely to be involved in the evolution of CML, and the more random “minor route” ACAs, which may denote nothing more than the instability of the genome.^{5,7} Mutations of the BCR-ABL tyrosine kinase domain are also seen in the majority of those in blast phase CML and, depending on the specific mutation, can negatively predict the response to certain TKI therapies.⁴

PROGNOSIS

The single most important prognostic indicator for patients with CML remains the length of response to initial BCR-ABL-specific TKI therapy.

Dr. Powers is a fellow and **Dr. Kambhampati** is an associate professor of medicine, both in the Department of Internal Medicine, Division of Hematology/Oncology, at the University of Kansas Medical Center in Kansas City, Kansas. Dr. Kambhampati is also a staff physician in the Hematology/Oncology Division at the Kansas City VAMC in Kansas City, Missouri.

Table 1. Definition of Response to BCR-ABL–Specific Tyrosine Kinase Inhibitors¹

Response	Testing	Results
MHR	CBC with differential	Normal differential, no peripheral blasts, no hepatosplenomegaly, persistent neutropenia, or thrombocytopenia
CHR	CBC with differential	Normal blood counts and differential, no peripheral blasts, no hepatosplenomegaly
MCyR	Cytogenetics (bone marrow) or I-FISH (peripheral blood)	< 35% Ph+ metaphases in ≥ 20 cells analyzed < 35% BCR-ABL–positive nuclei out of ≥ 200 cells
CCyR	Cytogenetics (bone marrow) or I-FISH (peripheral blood)	No Ph+ metaphases in ≥ 20 cells analyzed < 1% BCR-ABL–positive nuclei out of ≥ 200 cells
MMR	RT-Q-PCR (peripheral blood)	BCR-ABL transcript level ≤ 0.1%
CMR	RT-Q-PCR (peripheral blood)	BCR-ABL transcript level undetectable

Abbreviations: CBC, complete blood cell count; CCyR, complete cytogenetic response; CHR, complete hematologic response; CMR, complete molecular response; I-FISH, interphase fluorescence in situ hybridization; MCyR, major cytogenetic response; MHR, major hematologic response; MMR, major molecular response; Ph+, Philadelphia chromosome–positive; RT-Q-PCR, quantitative reverse transcriptase polymerase chain reaction.

Only a very small minority of patients are refractory to TKIs from the beginning; these are the patients with the worst prognosis.⁸ If the response to treatment seems inadequate, then the health care professional should first verify with the patient that he or she is taking the medicine as prescribed.¹ Lack of adherence continues to be the most common reason for less-than-ideal outcomes or fluctuations in response and plays a critical role in treatment with TKI therapy, with worse outcomes when < 90% of doses are taken.⁹

Other features associated with a poor prognosis include cytogenetic clonal evolution, > 50% blasts, and/or extramedullary disease.^{7,10,11} At the time of imatinib failure, detection of mutations of the BCR-ABL tyrosine kinase domain correlates to worse 4-year event-free survival.¹² Showing the instability of the genome in CML, patients who harbor mutations of the BCR-ABL domain have a higher likelihood of relapse associated with further mutations and, therefore, potentially further

TKI resistance.¹³ Once CML has progressed to the blast phase, life expectancy is, on average, less than a year.¹¹

TREATMENT STRATEGY

Currently, the most effective treatment strategy in blast phase CML is to prevent the transformation from chronic phase from ever occurring.

Management of blast phase CML depends on 2 factors: (1) previous therapies; and (2) type of blast phase—myeloid or lymphoid. The goal of treatment is to knock the disease back to a clinical remission and/or a chronic phase for a long enough period to get the patient to allo-SCT if age, performance status, and suitable donor allow for it.

Fast Facts...

- ▶ Blast phase CML can be defined by 30% blasts in the blood or bone marrow or the presence of extramedullary disease
- ▶ Prognosis remains poor; median overall survival is less than a year
- ▶ First-line treatment strategies include a BCR-ABL–specific TKI with conventional induction chemotherapy, depending on type of leukemia (myeloid or lymphoid), as determined by flow cytometric analysis
- ▶ The main goals of treatment are to induce chronic phase CML again, in hopes of proceeding to allogeneic stem-cell transplant soon thereafter if patient is a candidate
- ▶ The most effective way of treating blast phase CML is to never let the CML progress beyond the chronic phase

Table 2. Comparison of Trials of Single-Agent BCR-ABL–Specific Tyrosine Kinase Inhibitors (Other Than Imatinib) for Treatment of Blast Phase Chronic Myelogenous Leukemia

Drug	No. of Patients	Patient Characteristics	MHR	CyR
Nilotinib ¹⁵ (phase III)	N = 136 Myeloid, n = 105 Lymphoid, n = 31	- Failed only 1 TKI, imatinib - Best previous response with imatinib: 10% CHR, 11% MCyR - 54% had ACAs in addition to BCR-ABL fusion - 38% had BCR-ABL kinase domain mutations (3 patients with T315I mutation) - 14 patients went on to allo-SCT	Myeloid: 60% Lymphoid: 59%	Myeloid: 38% MCyR 30% CCyR Lymphoid: 52% MCyR 32% CCyR
Dasatinib ¹⁶ (phase III)	N = 210 Myeloid, n = 149 Lymphoid, n = 61	- Failed only 1 TKI, imatinib - Best previous response with imatinib unknown - 33% had BCR-ABL kinase domain mutations (6 patients with T315I mutation) - Not all who had CyR to dasatinib had corresponding hematologic response - 15 patients went on to allo-SCT	Myeloid: 28% Lymphoid: 38%	Myeloid: 27% MCyR 17% CCyR Lymphoid: 46% MCyR 37% CCyR
Ponatinib ¹⁷ (phase II)	N = 62 Myeloid, n = 52 Lymphoid, n = 10	- 95% previously used ≥ 2 BCR-ABL–specific TKIs 60% previously used ≥ 3 TKIs - 97% resistant to dasatinib and/or nilotinib - Most recent response to dasatinib or nilotinib: 15% MHR or better (11% MCyR, 3% MMR) - 45% had BCR-ABL kinase domain mutations, 16% had ≥ 2 kinase domain mutations (24 patients with T315I mutation)	Myeloid: 29% Lymphoid: 40%	Myeloid: 19% MCyR 15% CCyR Lymphoid: 40% MCyR 30% CCyR

Abbreviations: ACA, additional cytogenetic aberrations; allo-SCT, allogeneic stem cell transplant; CCyR, complete cytogenetic response; CHR, complete hematological response; CyR, cytogenetic response; MCyR, major cytogenetic response; MHR, major hematological response; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

^aData only for those with an MCyR.

^bData not separated by myeloid and lymphoid.

Using single-agent imatinib for blast phase CML has been tried in patients who have never been on TKI therapy before. Hematologic responses were seen in the majority of patients, but any form of cytogenetic response was seen in fewer than 20% of patients. Median overall survival, although better than with previous conventional chemotherapies, was still measured in months.⁶ A patient with blast phase CML who has never been on BCR-ABL–specific TKIs is very rare now; at a minimum, the patient has usually tried at least 1 TKI previously.

If blast phase CML develops while a patient is taking imatinib, treatment with a second-generation TKIs—nilotinib or dasatinib—should be attempted if the BCR-ABL tyrosine kinase domain analysis shows no resistant mutations.¹⁴ Both nilotinib and dasatinib have been tried as single agents in patients with imatinib-refractory CML or who are unable to tolerate imatinib.^{15,16} Cytogenetic response rates were 2 to 4 times higher for these agents than for imatinib when used in blast phase CML.

Table 1 (previous page) reviews

the common definitions of response, including cytogenetic response, to TKIs in CML. The pattern of response is usually very predictable: First, a hematologic response is seen, then a cytogenetic response, and finally, a hoped-for molecular response. Interestingly, in these studies, not all patients with blast phase CML who experienced a cytogenetic response had a hematologic response. This makes CBCs less reliable for assessing response and other peripheral blood tests, such as the interphase fluorescence in situ hybridization (I-FISH) test or the

	PFS	OS
	Myeloid ^a : Median: 10.8 mo 1-year: 48% 2-year: 44%	Myeloid: Median: 10.1 mo 1-year: 44% 2-year: 32%
	Lymphoid ^a : Median: 3.2 mo 1-year: 0%	Lymphoid: Median: 7.9 mo 1-year: 36% 2-year: 10%
	Myeloid: Median: 3.7 mo 1-year: 20% 2-year: 15%	Myeloid: Median: 7.8 mo 1-year: 36% 2-year: 25%
	Lymphoid: Median: 4.7 mo 1-year: 3% 2-year: 0	Lymphoid: Median: 10 mo 1-year: 42% 2-year: 18%
	Median ^b : 4 mo 1-year ^b : 19%	Median ^b : 7 mo 1-year ^b : 29%

quantitative reverse transcriptase polymerase chain reaction (RT-Q-PCR) test, more important. Unfortunately, this improved cytogenetic response in blast phase CML did not translate to long-term survival advantage; median survival with these second-generation TKIs was still less than a year without transplant. If the T315I mutation is present, then clinical trials involving ponatinib or one of the newest non-FDA-approved TKIs should be considered.

Recent data involving ponatinib suggest similar response and survival rates to nilotinib and dasatinib, but

this was in more heavily-pretreated CML patients who had resistance to, or unacceptable adverse effects from the second-generation TKIs or who had the BCR-ABL T315I mutation.¹⁷

In late 2013, ponatinib was voluntarily suspended from marketing and sales by its manufacturer due to a worrisome rate of serious arterial thromboembolic events reported in clinical trials and in postmarketing experience. However, the FDA reintroduced ponatinib in 2014 once additional safety measures were put in place, such as changes to the black box warning and review of the risk of arterial and venous thrombosis and occlusions.¹⁸

Table 2 compares the results between these newer TKIs in blast phase CML. If the patient can tolerate it, a combination of TKI with AML or ALL-type induction chemotherapy, preferably in a clinical trial setting, provides the best opportunity to return the patient to the chronic phase. If this is achieved, then allo-SCT represents the best chance for sustained remission or cure; allo-SCT was standard first-line therapy prior to the advent of BCR-ABL-specific TKIs. Tyrosine kinase inhibitor exposure prior to allo-SCT does not seem to affect transplantation outcomes.¹⁹ Allo-SCT while still in blast phase is discouraged because of its high risks with minimal benefit; disease-free survival rates are <10%.¹⁹ Although no scientific data support this, maintenance TKI posttransplantation seems logical, with monitoring of BCR-ABL transcript levels every 3 months.

CONCLUSION

With the advent of TKI therapy, the overall prognosis of CML has

changed drastically. Unfortunately, the success seen with these novel agents in the chronic phase of CML has not translated into success in the blast phase of CML. Therefore, the best way to manage blast phase CML is to prevent this transformation from ever happening. The deeper and more rapid the cytogenetic and molecular response after TKI initiation, the better the long-term outcome for the patient.

If the patient progresses through TKI therapy, then combining a different TKI with a conventional induction chemotherapy regimen for acute leukemia should be tried; the goal is to achieve a remission that lasts long enough for the patient to be able to undergo allo-SCT. If the patient is not a candidate for allo-SCT, then the prognosis is extremely poor, and clinical trials with best supportive care should be considered. ●

Author disclosures

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