Published in final edited form as:

Leuk Lymphoma. 2014 July ; 55(7): 1451–1462. doi:10.3109/10428194.2013.845883.

Potential mechanisms of disease progression and management of advanced-phase chronic myeloid leukemia

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Abstract

Despite vast improvements in treatment of Philadelphia chromosome–positive chronic myeloid leukemia (CML) in chronic phase (CP), advanced stages of CML, accelerated phase or blast crisis, remain notoriously difficult to treat. Treatments that are highly effective against CML-CP produce disappointing results against advanced disease. Therefore, a primary goal of therapy should be to maintain patients in CP for as long as possible, by (1) striving for deep, early molecular response to treatment; (2) using tyrosine kinase inhibitors that lower risk of disease progression; and (3) more closely observing patients who demonstrate cytogenetic risk factors at diagnosis or during treatment.

Keywords

myeloid leukemias and dysplasias; tyrosine kinase inhibitor; drug resistance

INTRODUCTION

The availability of selective BCR-ABL tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML) marked a major advance in the treatment of this cancer by prolonging survival in patients across all stages of disease severity: chronic phase (CP), accelerated phase (AP), and blast crisis (BC) [1,2,3]. Despite this, however, survival rates continue to be better for patients in CP than for patients in advanced stages of disease, AP or

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Potential Conflicts of Interest

Dr. Jabbour reports honoraria from Bristol-Myers Squibb, Novartis, and Pfizer, outside the submitted work. Dr. Hughes reports honoraria, consultancy, and research support from Bristol-Myers Squibb, Novartis, and Ariad, outside the submitted work. Dr. Cortes reports grants, consultancy, and research support from Ariad, grants and research support from Novartis, consultancy and research support from Pfizer, consultancy and research support from ChemGenex, grants and research support from Bristol-Myers Squibb, and research support from Deciphera, outside the submitted work. Dr. Kantarjian reports research support from Bristol-Myers Squibb, consultancy and research support from Novartis, and research support from Pfizer, outside the submitted work. Dr. Hochhaus reports consultancy, honoraria, and research support from Ariad, Novartis, Pfizer, Bristol-Myers Squibb, and Merck Sharpe & Dohme, outside the submitted work.

BC [1]. Decades of clinical and molecular research have led to the development of therapies that are highly effective in CML-CP, yet treatment options for CML-AP and -BC are limited and the clinical outlook for patients who progress to AP/BC remains bleak. Advances in the treatment of patients with CML-AP and -BC are hampered in part by factors such as the lack of uniform clinical criteria that define AP/BC and the array of genetic defects implicated in disease progression, which underscores the complexity of the disease in its advanced stages.

This review outlines the various definitions for CML-AP and CML-BC, describes potential mechanisms of disease transformation to AP/BC, discusses clinical factors associated with risk of disease progression, and provides an overview of clinical data on protection from progression and treatment options for patients in AP/BC.

DEFINITIONS OF CML-AP AND CML-BC

Over the years, several groups have outlined staging classification criteria that define CML-AP and CML-BC [4–8] (Table I). The set of criteria most often used in clinical studies of CML are those from the European Leukemia Net (ELN), which sets the threshold blast count for CML-BC at 30% [8]. World Health Organization criteria set the threshold blast count for CML-BC at 20%, in alignment with the clinical definition of acute myeloid leukemia (AML)[7]. Because patients with 20%–29% blasts have significantly better rates of complete cytogenetic response (CCyR) and 3-year overall survival (OS) than do patients with 30% blasts [9], they are classified as having CML-AP by criteria of both the ELN and the M. D. Anderson Cancer Center, Houston, TX [8,9]. Regardless of the criteria used to define BC, it should be recognized that blast count thresholds are arbitrary values, because blast count is a continuous variable [9]. Until a biological, evidence-based definition of BC is established, most clinicians will likely continue defining BC according to their own experiences [3].

POTENTIAL MECHANISMS OF DISEASE PROGRESSION IN CML

Disease progression to CML-BC is characterized by increased cell proliferation and arrested cell differentiation and apoptosis, pathologic features that must be accounted for by any model of disease progression. Although the role of BCR-ABL tyrosine kinase activity in the pathogenesis of CML is firmly established [10,11], its role in driving disease progression is less clear. Not all mechanisms implicated in disease progression in CML stem directly from BCR-ABL activity, although its involvement in the process is highly plausible. Here, we summarize potential mechanisms of disease progression in CML; a more comprehensive review of the topic can be found in Perrotti *et al* [12].

BCR-ABL Expression

The level of *BCR-ABL* gene expression has been shown to be associated with disease progression. An increase in *BCR-ABL* gene expression can arise from either an up regulation of mRNA levels or an increase in the number of CML cells in the blood. Studies of *BCR-ABL* transcript kinetics have not demonstrated conclusively that increased *BCR-ABL* expression is a causal event in the progression of CML to AP/BC [13,14]. Because increased

BCR-ABL expression precedes the manifestation of clinical or laboratory signs of AP/BC, however, it is thought to be at least an early event in disease progression.

BCR-ABL–Mediated Genetic Instability

The accumulation of chromosomal abnormalities and genetic defects is a hallmark of disease progression in CML. Among patients with demonstrable hematologic resistance or recurrence, additional cytogenetic abnormalities were more frequent in CML-BC patients than in CML-CP or CML-AP patients (73% versus 52% versus 50%, respectively) [15]. The greater prevalence of genetic instability in leukemic cells of patients with advanced disease arises from enhanced DNA damage and reduced capacity to repair that damage. Both BCR-ABL–dependent [16,17] and –independent [18] mechanisms of generating reactive oxygen species can contribute to overall genomic instability by inducing oxidative DNA damage such as double-strand breaks [19]. Furthermore, *in vitro* experiments have demonstrated that expression of BCR-ABL protein sensitizes cells to ionizing radiation [20] and causes cells to accumulate drug-induced DNA damage [21]. Indeed, *BCR-ABL* activity has been shown to (1) disrupt proteins involved in repair of DNA double-strand breaks [20] [22] [23]; (2) up regulate expression of BCL-xL [21], an antiapoptotic protein; and (3) cause cell-cycle arrest in G2/M in cells treated with DNA-damaging agents [21], actions that together can promote greater genomic instability.

This environment of genomic instability may explain the emergence of nonrandom chromosomal abnormalities (*i.e.*, clonal evolution) commonly observed with CML disease progression, although the precise etiology of these abnormalities is not known. The more common “major route” chromosomal abnormalities identified in patients in CML-BC include trisomy 8 (~40%), double Philadelphia (Ph) chromosome (~38%), and isochromosome i (17q) (~21%). Other common chromosomal abnormalities include trisomy 19 (~16%), trisomy 21 (~9%), monosomy 7 (~5%), and monosomy 17 (~4%)[24,25]. Although the pathologic link between these abnormalities and CML disease progression is not fully elucidated, there is some evidence that duplication/amplification of known oncogenes (*eg*, MYC on chromosome 8[26]) or loss of known tumor suppressor genes (*eg*, TP53 on chromosome 17[27]) that reside on affected chromosomes may contribute to disease progression.

RNA-Binding Proteins

The RNA-binding protein hnRNP A1 is over expressed in myeloid progenitor cells expressing BCR-ABL and in cells from patients with CML-BC [28]. *In vitro* experiments have shown hnRNP A1 to bind the mRNA of genes whose protein products are also regulated by BCR-ABL activity, suggesting a role for mRNA metabolism in leukemogenesis. The mRNA of SET, a phosphoprotein implicated in acute leukemia [29] is bound by hnRNP A1[30]. Importantly, SET is a potent inhibitor of protein phosphatase 2A (PP2A) [31], a serine/threonine phosphatase that functions as a tumor suppressor in CML (reviewed in Perrotti and Neviani [32]). *In vitro* studies have demonstrated both BCR-ABL–dependent inhibition of PP2A activity, mediated by upregulated protein expression of SET [30] and PP2A-dependent regulation of BCR-ABL activity and leukemogenic potential. The mutual antagonism of PP2A and BCR-ABL suggests that inactivation of PP2A might be an

early step in the blastic transformation of CML cells. In addition to SET, hnRNP A1 also binds to the transcription factor E2F3 in BCR-ABL-expressing cell lines and cells from patients with CML-BC [33]. Furthermore, E2F3 activity is required *in vitro* and *in vivo* for BCR-ABL oncogenic activity. Taken together, these findings highlight the role that mRNA metabolism plays in the post-transcriptional regulation of genes as a mechanism of disease progression in CML.

Centrosomal Aberrations

The centrosome is a eukaryotic cellular organelle that organizes the mitotic spindle and ensures the faithful bipolar separation of sister chromatids during mitosis and meiosis [34]. Defects in centrosome function can lead to chromosome missegregation, representing another potential cause of genomic instability observed in CML [35–37]. The prevalence of centrosomal aberrations correlates with disease stage in CML and with the degree of aneuploidy found in leukemic cells. These observations, viewed in light of evidence that BCR-ABL protein interacts with the centrosomal protein, pericentrin, suggests that BCR-ABL activity may in part cause and/or propagate centrosomal aberrations that result ultimately in loss of chromosomal integrity. Interestingly, treatment of CML patients with BCR-ABL TKIs and exposure of cells to TKIs can induce centrosomal aberrations in disease-unrelated cells, even as TKI treatment suppresses BCR-ABL activity in leukemic cells, suggesting that multiple pathways may be involved in the destabilization of centrosome activity [38]. At present, however, there is no conclusive evidence that TKI therapy in CML increases the risk of secondary cancers [39].

Telomere Length

Telomere length naturally decreases with cycles of cell division. When telomeres become critically short, they may be mistaken for double-strand DNA breaks, so normal somatic cells enter replicative senescence to prevent genomic instability [40]. In cancerous cells, telomere shortening and inappropriate telomerase activation are frequently observed [41]. The average telomere length of patients with CML is significantly shorter than that of age-matched healthy individuals [42,43]. Because average telomere length of patients in CML-AP/BC is significantly shorter than that of patients in CP [42,43] and telomere length significantly correlates with duration of CP [42], telomere shortening has been implicated in disease progression in CML. At present, the prognostic utility of telomere length as a predictive biomarker of disease progression in CML is under study (ClinicalTrials.gov identifier NCT01061177).

Studies of telomere function in mouse models and in primary cancer cells derived from patients show that telomerase dysfunction and telomere shortening promote chromosomal instability [44], [45]. Thus, defects in telomere maintenance could potentially amplify other mechanisms of chromosome instability in CML stemming from *BCR-ABL* activity. Because telomere length can be partially restored with imatinib treatment [46], a more direct role for *BCR-ABL* in regulating telomere length cannot be discounted.

Differential Gene Expression

Gene expression profiling studies have sought to identify a set of differentially expressed genes associated with disease stage and therefore likely responsible for progression, manifestation of phenotypes and genotypes characteristic of advanced disease, or both. As expected, expression of genes functionally related to cell-cycle regulation, transcription, myeloid differentiation, intracellular signal transduction, cell adhesion, apoptosis, and immune response have been found to be differentially altered in samples derived from patients in CML-BC compared with CML-CP [47–49]. Despite variations in methodology used in different studies (*eg*, sources of samples, array platforms), a number of genes were identified in multiple studies as BC-specific, and the functional roles of progression-related genes were similar across studies, giving credence to the overall findings of these studies in aggregate.

FACTORS SHOWN TO PREDICT DISEASE PROGRESSION

According to the German CML Study Group experience, the cumulative incidence of CML-BC before the advent of imatinib (1983–2002) ranged from 12% to 61%, depending on the treatment modality, and has fallen to 4% since 2002 [3]. First-line treatment of CML-CP with TKI therapy significantly lowers the rate of progression to AP/BC, compared with non-TKI therapy (Table II). In the International Randomized Study of Interferon and STI571 (IRIS), the rate of freedom from progression to AP/BC at 18 months was significantly higher in the imatinib group than in the interferon (IFN)- α plus cytarabine comparator group (96.7% versus 91.5%, $P < 0.001$) [50]. Long-term follow-up of patients in the imatinib group shows that most progression events occurred within the first 3 years of treatment [50–53] (Figure 1).

It is not unexpected that imatinib, a potent BCR-ABL inhibitor [71], averts disease progression significantly better than did previous standard therapy [3], given that BCR-ABL activity likely plays a role in promoting disease progression. By extrapolation, TKIs that provide greater clinical inhibition of BCR-ABL than imatinib might be expected to provide even greater protection from disease progression. Indeed, 3-year follow-up of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients (ENESTnd) study shows that the number of progressions (defined by ELN criteria for AP/BC) per year is significantly lower with nilotinib than with imatinib [55–57] (Table II), and recently presented 4-year follow-up data are consistent with this finding [72]. In addition, 2-year follow-up of the Dasatinib versus Imatinib in Patients with Newly Diagnosed CML-CP (DASISION) study shows that the number of progressions (defined by ELN criteria for AP/BC) per year is lower with dasatinib than with imatinib [65–67] (Table II). Preliminary 3-year follow-up data of the DASISION study confirm this [65]. Furthermore, with a minimum of 12 months' follow-up in the Bosutinib Efficacy and Safety in CML (BELA) study of bosutinib newly diagnosed patients with CML-CP, four and 10 on-treatment progression events (defined by ELN criteria for AP/BC) were observed with bosutinib and imatinib, respectively [70]. Bosutinib, however, is currently approved only for treatment of CML after failure of prior therapy. Whether a reduction in the incidence of disease progression with approved first-line TKIs, nilotinib and dasatinib will significantly improve

OS remains to be determined, and longer-term follow-up of the ENESTnd and DASISION studies are needed.

Treatment Response

Studies correlating the level of response to imatinib with long-term survival outcome have found that patients who respond favorably to imatinib, especially those who respond early in the treatment course, have significantly lower probabilities of an event (*eg*, death, loss of response, or progression to AP/BC) and of transformation to AP/BC than patients who do not respond as well to imatinib [51–53,73–79]. A correlation between level of response to TKI treatment and long-term outcome holds true for patients in late CP and AP, in terms of OS at 2 years [80] and relapse-free survival over more than 5 years of follow-up [81]. These findings imply that improving response rates and/or the degree of response—for example, with first-line nilotinib or dasatinib—could potentially improve progression outcome [76]. Although longer follow-up of clinical studies with the newer TKIs is needed to confirm this hypothesis, preliminary reports of landmark analyses of the ENESTnd study [82] and the DASISION study [83] indicate that the probability of disease progression to AP/BC is lower and the probability of achieving major molecular response (MMR) is higher for patients achieving *BCR-ABL* transcript level 10% versus >10% at 3 months.

BCR-ABL Mutational Status

The presence of non-silent genetic mutations that alter the *BCR-ABL* protein sequence has been linked to an increased probability of disease progression, most likely related to acquired resistance to TKI therapy. In a study of patients with imatinib failure who subsequently underwent allogeneic stem cell transplant, patients with baseline *BCR-ABL* mutation were significantly more likely to progress to AP/BC at the time of imatinib failure and have lower rates of event-free survival (EFS) and OS at 2 years than patients without [84]. The number of *BCR-ABL* mutations detected at the time of imatinib failure carries prognostic value in patients with CML-CP; rates of 4-year EFS were 56%, 49%, and 0% for patients with no mutations, one mutation, and more than one mutation, respectively [85]. The site of genetic mutation affects progression risk as well. Patients with mutations in the ATP phosphate-binding loop (P-loop) were at higher risk of disease progression to AP/BC [86] and death due to disease progression [87], and had worse estimates of progression-free survival (PFS) [86], than patients with *BCR-ABL* mutations outside of the P-loop. Given that imatinib, nilotinib, and dasatinib binding to *BCR-ABL* affects the conformation of the P-loop, genetic mutations in the P-loop that allow bypass of TKI-mediated inhibition could restore *BCR-ABL* kinase activity [88] and account for the observed increase in progression risk associated with P-loop mutations.

Early concerns that treatment with the newer TKIs nilotinib and dasatinib would lead to selection for TKI-resistant *BCR-ABL* mutations have been largely assuaged. In the ENESTnd study, post-baseline mutational analysis done on patients with lack of response or loss of response and at the end of treatment detected newly emergent *BCR-ABL* mutations in 11 patients in the nilotinib 300 mg twice daily (BID) group, 11 in the nilotinib 400 mg BID group, and 21 in the imatinib group. Among these patients, the multi-TKI-resistant T315I mutation was detected in three, two, and three patients, respectively [89]. In the DASISION

study, post-baseline mutational analysis was done only in patients who discontinued treatment for any reason. New *BCR-ABL* mutations were detected in 10 patients each in the dasatinib and imatinib arms. Of these, seven of 10 patients in the dasatinib arm carried the T315I mutation, compared with no patients in the imatinib arm [67].

Cytogenetic Aberrations at Diagnosis

The effect of additional cytogenetic aberrations (ACAs) at diagnosis of CML on treatment response and survival outcomes was studied in 1151 patients enrolled in the German CML Study IV. Stratification of patients by type of cytogenetic aberration—standard t(9;22), variant t(v;22), lack of the Y chromosome (–Y), minor route, and major route—revealed a significant adverse effect of major-route aberrations at diagnosis on 5-year PFS (90% versus 81% versus 88% versus 96% versus 50%, $P<0.001$) and OS (92% versus 87% versus 91% versus 96% versus 53%, $P<0.001$) [90]. These findings corroborate others showing similarly that the presence of ACAs, particularly major-route aberrations, at diagnosis is associated with lower rates of PFS and OS at 2 years [91] and at 5 years [78]. Thus patients with major-route aberrations at diagnosis may benefit from closer evaluation or more intensive therapy.

Risk Score at Baseline

Two commonly used formulas to predict prognosis are the Sokal and the Hasford risk scores [92,93]. In the IRIS study, patients in the imatinib group with low Sokal score at baseline had significantly better 6-year survival without progression to AP/BC (93.9% versus 76.3%, $P<0.001$) than patients with high Sokal score [53]. In another study of 134 consecutive patients with CML-CP treated at a single center, patients with low/intermediate risk score by either Sokal or Hasford risk stratification at baseline had significantly better PFS during the study than patients with corresponding high risk score [94].

Recently, the European Treatment and Outcome Study for CML (EUTOS) developed a new formula to predict prognosis, the EUTOS score [95]. In the validation study of the EUTOS score, patients with low EUTOS score had significantly better 5-year PFS than patients with high EUTOS score [95]. Others have confirmed the value of the EUTOS score for predicting PFS [96] and EFS [97] in patients with CML treated with first-line imatinib, while others have not [98].

TREATMENT OPTIONS IN CML-AP/BC

Because advanced-phase CML is a complex disease, consensus on an optimal treatment approach has not been achieved. The following information on treatment options is based on that available from clinical practice guidelines, published literature, and our own clinical practices. Treatment options for patients with CML-AP/BC may include TKI therapy, allogeneic hematopoietic stem cell transplant (HSCT), chemotherapy, and other treatment modalities, such as IFN- α . When and in what sequence or combinations these treatment options are administered largely depends on the stage of disease, clinical presentation, and clinician experience.

TKI Therapy

All five currently available TKIs are approved in the US and Europe for treatment of CML-AP, and all but nilotinib are also approved for treatment of CML-BC [99–103]. Although TKI therapy is moderately effective in patients with CML-AP/BC, the overall effectiveness of TKI therapy in advanced CML is less robust than that observed in early-stage disease (Table III). We and others agree that TKI therapy should be considered a “bridge” to get patients with advanced CML to HSCT [3,104]. If HSCT is not offered, we recommend close monitoring by molecular testing every 3 months. Patients demonstrating a confirmed five-fold increase in *BCR-ABL* transcript levels and/or loss of MMR should be referred for HSCT.

Patients harboring the T315I mutation may benefit from treatment with ponatinib [126]. Preliminary reporting of the phase 2 Ponatinib Ph+ Acute Lymphoblastic Leukemia (ALL) and CML Evaluation (PACE) study showed that CCyR was achieved in 4 of 17 (24%) evaluable patients with CML-AP and in 12 of 41 (29%) evaluable patients with CML-BC or Ph+ ALL with the T315I mutation [125].

Patients who fail treatment with or who develop resistance to currently available TKIs may soon have another BCR-ABL TKI as a treatment option. Rebastinib (formerly DCC-2036) is a BCR-ABL TKI that, like ponatinib, has activity against the T315I mutation [127]. In a phase 1 study of 30 patients, including eight in CML-AP and three in CML-BC, rebastinib elicited hematologic responses in two patients with CML-AP [128].

Hematopoietic Stem Cell Transplant

Long-term remission is uncommon in advanced CML, but HSCT represents the best option for patients in advanced stages of CML to achieve remission or cure. Unfortunately, HSCT is associated with both considerable morbidity and the need for subsequent immunosuppressive therapy to modulate graft-versus-host disease, so this procedure is generally reserved for patients younger than 65 years of age with relatively good performance status who have an available donor. Considering that the median age of diagnosis of CML is 64 years [129], the role of HSCT is limited. The identification of potential matching donors can be a time-consuming process; thus, clinicians who are considering HSCT for their patients should refer them for evaluation for HSCT before their health status precipitously declines [3,104]. Consistent with observed trends in efficacy with other treatment modalities, long-term outcomes following HSCT are better for patients who undergo the procedure in CML-CP than in CML-AP/BC. In a subanalysis of the German CML Study IV, 3-year survival rate after HSCT was 91% for 56 patients who underwent the procedure while in CML-CP and 59% for 28 patients in CML-AP/BC (25 of 28 patients were in CML-BC)[130]. Notably, another study of outcomes after HSCT found that patients in second CP before transplant had survival outcomes at 3 years that were comparable to that of patients in AP and more favorable than that of patients in BC [131]. Following HSCT, we recommend maintenance therapy with a TKI (selected based on previous response and mutation profile) and molecular monitoring every 3 months.

Newly Diagnosed Advanced CML

For patients who are newly diagnosed with CML-AP/BC or have signs that may indicate high risk of progression to AP/BC (*eg*, high Sokal or Hasford risk score, unfavorable cytogenetics), we recommend that they be treated intensively. Treatment of patients with CML-AP with nilotinib (400 mg BID) or dasatinib (140 mg once daily [QD]) has been recommended [132]. For patients with CML-BC who have been pretreated with conventional therapy, such as IFN- α or hydroxyurea, but not with TKIs, treatment with high-dose imatinib (600–800 mg QD), dasatinib (140 mg QD), or nilotinib (400 mg BID) are all valid options [3]. Patients with CML-AP or CML-BC should be referred for evaluation of eligibility for HSCT [133].

Progression to Advanced CML

For patients who progress to CML-AP/BC while on first-line TKI therapy, median OS is short, approximately 10.5 months for both imatinib and nilotinib [56]. We consider that a switch in treatment to an alternative TKI is appropriate for patients who progress to CML-AP while on imatinib (Table III). The choice of second-line TKI should depend in part on *BCR-ABL* mutational status. *In vitro* evidence shows that TKIs have differential binding affinity for common *BCR-ABL* kinase domain mutations [134], although it should be acknowledged that *in vitro* binding affinity by itself is insufficient to predict clinical activity [135]. Depending on response to TKI treatment, patients may be considered for HSCT [132].

For patients progressing to CML-BC following prior imatinib, treatment with nilotinib or dasatinib (depending on mutational status) in combination with acute leukemia-type chemotherapy is a viable option [3,132]. Patients with lymphoid BC may be treated with ALL-type induction chemotherapy, and those with myeloid BC with AML-type induction therapy [132]. If TKI-based therapy fails, then treatment with an ALL-type or AML-type induction chemotherapy regimen, depending on the leukemia subtype, or enrollment in a clinical study is recommended [3].

Patients with CML-BC with extramedullary infiltration have particularly poor prognosis [136,137]. There is no standard treatment for CML-BC with extramedullary involvement. Treatment with either chemotherapy regimens or imatinib has been shown to yield comparable outcomes, in terms of response and duration of response [138]. For cases in which extramedullary infiltration involves the central nervous system, however, evidence suggests that imatinib treatment may not be appropriate. Both in humans and other primates, imatinib concentrations in cerebrospinal fluid is much lower than in plasma [139–142], suggesting that imatinib may not cross the blood-brain barrier. At present, studies of the pharmacokinetics of other TKIs in cerebrospinal fluid are lacking.

TKI-Based Combination Regimens

Although allogeneic HSCT remains the gold standard for patients in CML-BC after complete remission with induction chemotherapy and TKIs, a recent report has shown improved OS among patients with Ph+ ALL who achieved MMR or better after induction chemotherapy plus imatinib or dasatinib and did not undergo HSCT [143]. These findings

suggest that long-term survival without HSCT may be possible in patients who achieve deep molecular response to induction chemotherapy plus TKIs. In addition, patients who achieved MMR in this study at 3, 6, 9, and 12 months had significantly better OS than patients who did not [143], findings that support the prognostic value of achieving deep response at those timepoints and underscore the importance of molecular monitoring every 3 months in patients with advanced disease.

Various combination regimens of imatinib plus chemotherapy have been evaluated in clinical studies [144–148]. Generally, the rationales for these combinations include: (1) agents in combination may overcome resistance of leukemia cells to single agents; (2) combining agents with distinct mechanisms of action may delay clonal selection of resistant leukemia cells; (3) combination regimens may elicit responses more rapidly than single agents, allowing patients to be referred to HSCT sooner; (4) combination regimens may enhance elimination of quiescent leukemic stem cells.

Several studies have found that TKI-based combination induction regimens followed by HSCT can be effective in prolonging OS. In one study of imatinib plus mitoxantrone/etoposide/cytarabine in 16 patients with CML-BC, seven patients who received the more intensive induction regimen achieved hematologic response, and four of seven subsequently underwent HSCT. Of these four patients, three remained in CCyR and achieved sustained negativity as shown by polymerase chain reaction for at least 9–28 months after HSCT [146]. In another study of imatinib plus omacetaxine/granulocyte colony-stimulating factor in 11 patients with CML-BC after imatinib failure, major cytogenetic response was achieved in 100% of patients. Eight patients proceeded to HSCT, and six patients were alive, including five with complete hematologic response (CHR), a median of 12 months later [147]. Studies of anthracyclines plus imatinib/cytarabine combinations have also shown clinical activity in CML-BC. In one such study, an induction regimen of daunorubicin plus imatinib/cytarabine was evaluated in 36 patients with myeloid CML-BC. Twenty patients achieved CHR, half of whom underwent HSCT thereafter. Median OS for patients who achieved hematologic response was 35.4 months [148]. In another study, treatment of 19 patients with myeloid CML-BC with idarubicin plus imatinib/cytarabine resulted in CHR for nine patients, including CCyR in three patients. Six patients underwent HSCT. Median survival was 5 months [149].

CONCLUSIONS

The advent of BCR-ABL TKI therapy has vastly improved the clinical outlook for patients with CML. Patients with advanced CML fare better today than at any other time in history; nonetheless, there remains considerable room for improvement. The number of effective treatment options is limited in advanced CML, and treatment modalities effective in CML-CP are not nearly so in CML-AP/BC. Clinical studies of currently approved therapies, investigational agents, and combination regimens continue unabated with the goal of expanding the number of treatment options available to patients in CML-AP/BC.

The approval in the US and Europe of nilotinib, dasatinib, bosutinib, and ponatinib for advanced CML provides clinicians with multiple treatment options for patients with CML-

AP/BC, although treatment response to TKIs in late-stage disease is not as favorable as in early CP. As such, our view is that a prudent approach to clinical practice is to stably maintain patients in CML-CP for as long as possible [3,104]. The treating clinician can accomplish this goal of therapy by optimizing response to first-line therapy and by monitoring for the presence of clonal evolution, which portends poor prognosis.

Regarding optimal first-line therapy, the higher rates of molecular response and lower rates of progression with nilotinib and dasatinib compared with imatinib indicate that the use of the newer TKIs for first-line treatment may improve overall survival of patients in CML-CP, in part by effectively preventing disease progression. In this regard, longer-term survival data from clinical studies of first-line TKI treatment are eagerly awaited.

Regarding clonal evolution, its presence at diagnosis predicts shortened PFS and OS, and its occurrence during treatment is considered a marker of treatment failure. Thus, clinicians can consider for closer observation and/or more intensive therapy patients who demonstrate high-risk cytogenetic features at diagnosis or inadequate response to first-line treatment. Adopting such a proactive approach in treating patients showing early signs of potential disease progression will reduce the likelihood of disease progression.

Acknowledgments

Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. The authors thank Anna Lau, PhD, and Patricia Segarini, PhD, of Percolation Communications LLC for their medical editorial assistance.

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Figure 1.
Annual rate of progression to CML in accelerated phase or blast crisis for patients treated with imatinib in the IRIS study [51–53].

Table I

Staging classification criteria for CML [7–9]

Disease stage	ELN criteria	MDACC criteria	WHO criteria
Chronic phase	<ul style="list-style-type: none"> None of the criteria for accelerated phase or blast crisis 	<p>High risk</p> <ul style="list-style-type: none"> Platelets $> 1000 \times 10^9/L$ before therapy Clonal evolution not present at diagnosis but develops during the course of therapy <p>Low risk</p> <ul style="list-style-type: none"> Blasts $< 10\%$ in peripheral blood or bone marrow Basophils $< 20\%$ in peripheral blood or bone marrow Clonal evolution present at diagnosis but does not progress during the course of therapy 	<ul style="list-style-type: none"> White blood cell count $20 \times 10^9/L$ Blasts $< 10\%$ Peripheral blood basophils $< 20\%$
Accelerated phase	<ul style="list-style-type: none"> Blasts 15%–29% in blood or bone marrow; blasts plus promyelocytes $> 30\%$ in blood or bone marrow, with blasts $< 30\%$ Basophils 20% in blood Persistent thrombocytopenia ($< 100 \times 10^9/L$) unrelated to therapy 	<ul style="list-style-type: none"> Blasts 10%–29% in peripheral blood or bone marrow Blasts plus promyelocytes 30% Basophils 20% in peripheral blood or bone marrow Platelets $< 100 \times 10^9/L$ unrelated to therapy Persistent splenomegaly, white blood cell count $> 10 \times 10^9/L$, or platelets $> 1000 \times 10^9/L$ unresponsive to sustained therapy 	<ul style="list-style-type: none"> Blasts 10%–19% of white blood cells in peripheral and/or nucleated bone marrow cells Peripheral blood basophils 20% Persistent thrombocytopenia ($< 100 \times 10^9/L$) unrelated to therapy or persistent thrombocytosis ($1000 \times 10^9/L$) unresponsive to therapy Increasing spleen size and increasing white blood cell count unresponsive to therapy Cytogenetic evidence of clonal evolution
Blast crisis	<ul style="list-style-type: none"> Blasts 30% in blood or bone marrow Extramedullary blast involvement 	<ul style="list-style-type: none"> Blasts 30% in peripheral blood or bone marrow Extramedullary blastic disease 	<ul style="list-style-type: none"> Blasts 20% of peripheral blood white cells or nucleated bone marrow cells Extramedullary blast proliferation Large foci or clusters of blasts in the bone marrow biopsy

Abbreviations: ELN, European Leukemia Net; MDACC, MD Anderson Cancer Center; WHO, World Health Organization

Table II

Progressions reported in clinical studies of imatinib, nilotinib, and dasatinib

Study	Drug treatment(s)	Patients, N	Timepoint	Cumulative progressions to AP/BC, n
IRIS [50–53]	Imatinib 400 mg vs IFN- α + cytarabine	IM: 553 IFN + cytarabine: 553	12 months	8* 33
		IM: 461	2 years	22
		IM: 431	3 years	29
		IM: 409	4 years	33
		IM: 382	5 years	35
		IM: 364	6 years	35
		NA	7 years	35
		IM: 304	8 years	36
German CML Study IV [54]	Imatinib 400 mg vs imatinib 800 mg vs imatinib + IFN- α	IM 400 mg: 325 IM 800 mg: 338 IM + IFN: 351	Median follow-up: IM 400 mg: 43 months IM 800 mg: 28 months IM + IFN: 48 months	IM 400 mg: 16 [†] IM 800 mg: 21 [†] IM + IFN: 12 [†]
ENESTnd [55–57]	Nilotinib 300 mg BID vs nilotinib 400 mg BID vs imatinib 400 mg	NIL 300 mg: 282 NIL 400 mg: 281 IM: 283	12 months of follow-up	NIL 300 mg: 2 [‡] NIL 400 mg: 1 [‡] IM: 11
		NIL 300 mg: 261 NIL 400 mg: 266 IM: 261	24 months of follow-up	NIL 300 mg: 2 [§] NIL 400 mg: 3 [§] IM: 12
		NIL 300 mg: 200 NIL 400 mg: 207 IM: 175	3 years of follow-up	NIL 300 mg: 2 [#] NIL 400 mg: 3 [#] IM: 12
MDACC [58,59]	Nilotinib 400 mg BID	61	Median 17.3 months of follow-up	2
		100	Median 24 months of follow-up	2
GIMEMA [60,61]	Nilotinib 400 mg BID	73	Median 15 months of follow-up	1
		73	Median 48 months of follow-up	1
ICORG 0802 [62–64]	Nilotinib 300 mg BID	15	Median 70 days of follow-up	0
		27 enrolled 18 evaluable	8 months	0
		61 enrolled 31 evaluable	12 months	0
DASISION [65–67]	Dasatinib 100 mg vs imatinib 400 mg	DAS: 259 IM: 260	12 months of follow-up	DAS: 5 IM: 9
		DAS: 199 IM: 194	24 months of follow-up	DAS: 6 IM: 13
MDACC [68]	Dasatinib 100 mg QD or 50 mg BID	62	Median 24 months of follow-up	0

Study	Drug treatment(s)	Patients, N	Timepoint	Cumulative progressions to AP/BC, n
SWOG 0325 [69]	Dasatinib 100 mg vs imatinib 400 mg	DAS: 123 IM: 123	Median 3 years of follow-up	DAS: 1 IM: 2
BELA [70]	Bosutinib 500 mg vs imatinib 400 mg	BOS: 250 IM: 252	12 months of follow-up	BOS: 4 IM: 10

Abbreviations: AP, accelerated phase; BC, blast crisis; BID, twice daily; BOS, bosutinib; DAS, dasatinib; IFN, interferon; IM, imatinib; NIL, nilotinib

* $P < 0.001$ versus control arm.

[†] Progression defined as disease progression to AP/BC or death from any cause.

[‡] Time to progression to AP/BC significantly lower versus control arm.

[§] Probability of progressing to AP/BC significantly lower versus control arm.

[#] Rate of progression to AP/BC significantly lower versus control arm.

Table III

Summary of clinical studies of TKIs in CML-AP and/or CML-BC

Study	TKI treatment	Patients*	CHR, %	CCyR, %	OS and/or PFS
Kantarjian 2002 [105]	Imatinib 400 or 600 mg	AP; N = 237 (n = 200 evaluable)	80.0	23.5	18-month OS: 73%
Talpaz 2002 [106]	Imatinib 400 or 600 mg	AP; N = 181	33.7**	16.6	12-month OS: 74%
Palandri 2009 [107]	Imatinib 600 mg	AP; N = 111	71.2**	20.7	Median OS: 37 months 7-year OS: 43%
Druker 2001 [108]	Imatinib 300–1000 mg	MyBC; n = 38 LyBC or ALL; n = 20	MyBC: 10.5 LyBC or ALL: 20.0	NR	NR
Kantarjian 2002 [109]	Imatinib 300–1000 mg	MyBC; n = 65 LyBC; n = 10	MyBC: 23.1 LyBC: 10.0	MyBC: 4.6 LyBC: 10.0	Median OS: MyBC: 6.5 months LyBC: 7 months
Sawyers 2002 [110]	Imatinib 400 or 600 mg	BC; N = 229	7.9**	7.4	Median OS: 6.9 months
Sureda 2003 [111]	Imatinib 600 mg	BC; N = 30	33.3**	0	1-year OS: 36%
Palandri 2008 [112]	Imatinib 600 mg	MyBC; n = 72 LyBC; n = 20	MyBC: 23.6** LyBC: 35.0	MyBC: 6.9 LyBC: 20.0	Median OS: 7 months
le Coutre 2008 [113]	Nilotinib 400 mg BID	AP; N = 119	26.1	16.0	12-month OS: 79%
Giles 2010 [114]	Nilotinib 400 mg BID	AP; N = 21 [†] (n = 17 evaluable)	0	0	6-month PFS: 57% 6-month OS: 80% 12-month OS: 80%
Kantarjian 2006 [115]	Nilotinib up to 1200 mg	AP; n = 56 MyBC; n = 24 LyBC; n = 9 [‡]	AP: 46.4 MyBC: 8.3 LyBC: 0	AP: 14.3 MyBC: 4.2 LyBC: 11.1	NR
Nicolini 2012 [116]	Nilotinib 400 mg BID	AP; n = 181 MyBC; n = 133 LyBC; n = 50 BC [‡] ; n = 7	AP: 22.1 MyBC: 6.8 LyBC: 14.0	AP: 11.0 MyBC: 8.3 LyBC: 26.0	18-month OS: AP: 81% MyBC: 62% LyBC: 66%
Giles 2012 [117]	Nilotinib 400 mg BID	MyBC; n = 105 LyBC; n = 31	MyBC: 60 [§] LyBC: 59 [§]	MyBC: 30 LyBC: 32	Median OS: MyBC: 10.1 months LyBC: 7.9 months
Guilhot 2007 [118]	Dasatinib 70 mg BID	AP; N = 107	39.3	24.3	8-month PFS: 76%
Apperley 2009 [119]	Dasatinib 70 mg BID	AP; N = 174	44.8	31.6	12-month PFS: 66% 12-month OS: 82%
Kantarjian 2009 [120]	Dasatinib 140 mg QD vs 70 mg BID	AP, QD/BID; n = 158/159	QD/BID: 47.5/51.5	QD/BID: 32.3/32.7	Median PFS, QD/BID: 25.1/26.0 months Median OS, QD/BID: not reached/ 30.7 months

Study	TKI treatment	Patients*	CHR, %	CCyR, %	OS and/or PFS
Talpaz 2006 [121]	Dasatinib 50–100 mg BID	AP: n = 11 MyBC: n = 23 Ly BC or ALL: n = 10 [†]	AP: 45.5 MyBC: 34.8 LyBC or ALL: 70.0	AP: 18.2 MyBC: 26.1 LyBC or ALL: 30.0	NR
Cortes 2007 [122]	Dasatinib 70 mg BID	MyBC: n = 74 LyBC: n = 42	MyBC: 25.7 LyBC: 26.2	MyBC: 27.0 LyBC: 42.9	Median PFS: MyBC: 5.0 months LyBC: 2.8 months
Cortes 2008 [123]	Dasatinib 70 mg BID	MyBC: n = 109 LyBC: n = 48	MyBC: 26.6** LyBC: 29.2	MyBC: 25.7 LyBC: 45.8	Median PFS/OS: MyBC: 6.7/11.8 months LyBC: 3.0/5.3 months
Saglio 2010 [124]	Dasatinib 140 mg QD vs 70 mg BID	QD/BID: MyBC: n = 75/74 LyBC: n = 33/28	QD/BID: MyBC: 17.3/17.6 LyBC: 21.2/14.3	QD/BID: MyBC: 13.9/21.1 LyBC: 37.5/36.0	Median OS, QD/BID: MyBC: 7.9/7.7 months LyBC: 11.4/9.0 months
Bosutinib 2012 [102]	Bosutinib 500 mg QD	AP: n = 76 BC: n = 64	AP: 30.4 BC: 15.0	NR	NR
Cortes 2012 [103]	Ponatinib 2 mg, 8 mg, 15 mg, 30 mg, 45 mg, or 60 mg QD	AP: n = 9 BC: n = 8 ALL: n = 5	AP/BC/ALL (N = 22): CHR: NA Major HR: 36	AP/BC/ALL (N = 22): CCyR: 14	NR
Cortes 2012 [#87 ASCO 2012 #6503]	Ponatinib 45 mg QD	AP: n = 79 BC or ALL: n = 94	Major HR: AP: 67 BC or ALL: 37	AP: 17 BC or ALL: 28	NR

Abbreviations: ALL, acute lymphoblastic leukemia; AP, accelerated phase; BID, twice daily; CCyR, complete cytogenetic response; CHR, complete hematologic response; LyBC, lymphoid blast crisis; MyBC, myeloid blast crisis; NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; QD, once daily; TKI, tyrosine kinase inhibitor

* All studies of nilotinib, dasatinib, bosutinib, and ponatinib in this table involved patients who had prior imatinib therapy.

** Response lasting 4 weeks.

[†] This study also included patients with CML-CP, results for whom are not described in this table.

[‡] Subtype of BC (myeloid or lymphoid) was unknown for seven patients.

[§] Rate of major hematologic response, which includes CHR and partial hematologic response.