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Use of Second- and Third-Generation Tyrosine Kinase Inhibitors in the Treatment of Chronic Myeloid Leukemia: An Evolving Treatment Paradigm

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Abstract

Although imatinib remains the gold standard for first-line treatment of chronic myeloid leukemia (CML), increasing recognition of imatinib resistance and intolerance has led to the development of additional tyrosine kinase inhibitors (TKIs), which have demonstrated effectiveness as salvage therapies or alternative first-line treatments. While additional options represent progress in the field, the availability of 3 second-generation TKIs (dasatinib, nilotinib, and bosutinib) and 1 third-generation TKI (ponatinib) has added complexity to the treatment paradigm for CML, particularly CML in chronic phase. Two second-generation agents (dasatinib and nilotinib) are approved for use as first-line and subsequent therapy. Thus, the appropriate sequencing of TKIs is a frequent quandary, and is incompletely addressed in clinical guidelines. Here, we review studies that may guide selection of a second- or third-generation TKI following TKI failure in patients with chronic-phase CML. These studies evaluate prognostic factors such as first-line cytogenetic response and *BCR-ABL1* mutation status, which may help physicians identify patients who are likely to respond to second-generation TKIs, as well as those for whom ponatinib or an investigational agent may be more appropriate. We summarize evidence to date suggesting that use of a second-generation TKI as third-line therapy confers limited value in most CML patients, and we also explore the utility of current event-free survival versus traditional outcomes to predict long-term benefits of sequential TKI use. Finally, we present 3 case studies to illustrate how prognostic factors and other considerations (eg, tolerability) can be used to individualize subsequent therapy in cases of TKI resistance or intolerance.

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Conflict of Interest

Dr Jabbour has received honoraria from ARIAD Pharmaceuticals, Inc., Pfizer, Bristol-Myers Squibb, Novartis, and Teva, outside the submitted work; Dr Kantarjian has received research grants from Novartis, Bristol-Myers Squibb, Pfizer, and ARIAD Pharmaceuticals, Inc., outside the submitted work; Dr Cortes reports grants and personal fees for consulting from ARIAD Pharmaceuticals, Inc., Bristol-Myers Squibb, Novartis, Pfizer, and Teva, outside the submitted work.

Keywords

Resistance; prognosis; response; outcome; BCR-ABL1

Introduction

Chronic myeloid leukemia (CML) accounts for an estimated 11% of new cases of leukemia[1] and is cytogenetically characterized by the Philadelphia (Ph) chromosome. The Ph chromosome is an abnormality resulting from a reciprocal translocation between chromosomes 9 and 22 and is present in at least 90% of CML cases.[2,3] The *BCR-ABL1* oncogene, a product of the Ph chromosome, encodes a chimeric BCR-ABL1 protein with constitutively active ABL1 tyrosine kinase activity, and the expression of *BCR-ABL1* in hematopoietic stem cells induces CML.[4] Imatinib, approved in 2001, inhibits the BCR-ABL1 tyrosine kinase and remains the gold standard for first-line treatment of Ph chromosome–positive (Ph+) leukemias. However, increasing recognition of imatinib resistance and intolerance has led to the development of additional tyrosine kinase inhibitors (TKIs) for the treatment of CML.

The most-studied mechanisms of imatinib resistance involve point mutations in the ABL1 kinase domain and overexpression of *BCR-ABL1*,[5] although research has also implicated BCR-ABL1–independent mechanisms such as upregulation of SRC kinases in some cases of imatinib failure.[6] The second-generation TKIs dasatinib, nilotinib, and bosutinib demonstrate enhanced inhibitory potency toward BCR-ABL1 and have shown efficacy in patients who developed BCR-ABL1 kinase domain mutations while receiving imatinib.[7–9] However, these second-generation TKIs may still fail because of resistance or intolerance. The BCR-ABL1 T315I mutation is insensitive to all second-generation TKIs,[7–9] and it is possible that sequential treatment with TKIs may cause selection of this and other mutations.[10,11] Sequential TKI therapy may also result in selection of cells harboring multiple drug-resistant BCR-ABL1 mutations, which may demonstrate increased oncogenic potency relative to their component mutants.[11,12]

Characteristics and indications for each of the 5 TKIs with marketing approvals for the treatment of CML are summarized in Table 1.[13–27] Although these TKIs differ with respect to target selectivity, pharmacokinetic profiles, dosing instructions, and unique toxicities, precise roles for each TKI in the management of CML are far from defined. Recent labeling changes have added complexity to the CML treatment paradigm, particularly with regard to CML in the chronic phase (CP). Imatinib is approved for first-line treatment of CP-CML and for CML of all phases after failure of interferon alfa therapy.[14,15] Although dasatinib[17,18] and nilotinib[20,21] were initially approved for the treatment of CML patients who are resistant or intolerant to imatinib, these second-generation TKIs later garnered indications for newly diagnosed CP-CML. Bosutinib is indicated for CML patients with resistance or intolerance to prior therapy.[23,24] In late 2013, the US indication for ponatinib, the third-generation TKI with unique activity against the T315I mutant, was revised to include only adults with T315I-positive CML (chronic, accelerated, or blast phase) or T315I-positive Ph+ acute lymphoblastic leukemia (ALL) and adults with CML (chronic, accelerated, or blast phase) or Ph+ ALL for whom no other TKI is indicated.[26] The European label remains broader.[27]

Sequencing of TKIs is further complicated by the fact that no TKI is specifically indicated for treatment of CML after failure of both first- and second-generation TKIs (ie, for third-line treatment). This manuscript will focus on prognostic factors for outcomes and response in CP-CML patients receiving second-generation TKIs after resistance or intolerance to first-line treatment. Three case studies provide examples of the use of these prognostic factors and other considerations to individualize CML care with second- and third-generation TKIs.

Sequential TKI Therapy in CP-CML

Second-Generation TKIs

The second-generation TKIs nilotinib and dasatinib were initially indicated for second-line treatment of CML following imatinib resistance or intolerance. In subsequent clinical trials, nilotinib[28–30] and dasatinib[31–33] showed responses more robust than those observed with imatinib in patients with newly diagnosed CP-CML, and indications for both were expanded to include first-line therapy.[17,18,20,21] One concern about the use of second-generation TKIs in the first-line setting is the uncertainty surrounding choice of second-line therapy. Limited information is available regarding responses rates with subsequent therapy after failure of dasatinib or nilotinib in the first-line setting. In one study of 218 CML patients who received dasatinib or nilotinib as first-line therapy, 40 (18%) discontinued therapy for a variety of reasons (adverse events, loss of response, and personal reasons) after a median follow-up of 23 months, and 19 (48%) of these 40 patients achieved a complete cytogenetic response (CCyR) or better on second-line therapy.[34] Because patients received a variety of second-line therapies (including imatinib, nilotinib, dasatinib, ponatinib, chemotherapy plus dasatinib, hematopoietic stem cell transplantation [HSCT], and bafetinib), no conclusions could be drawn regarding the response rates resulting from any particular second-line therapy after first-line nilotinib or dasatinib failure. However, results from prospective and retrospective studies evaluating second-generation TKIs (dasatinib, nilotinib, and bosutinib) in the third-line setting, following failure of imatinib and another second-generation TKI, showed lower response rates. These studies are summarized in Table 2, along with third-line data for ponatinib.[35–42] The optimal sequencing of second-generation TKIs cannot be determined from these reports because none prospectively compared different sequencing strategies and not all potential TKI sequences were evaluated. What is apparent from these studies is that use of a second-generation TKI as third-line therapy appears to have modest clinical benefit. Major cytogenetic response (MCyR) generally occurred in 30% to 50% of patients with CP-CML, was less likely to occur in patients who had resistance (vs intolerance) to second-line therapy, and was not necessarily durable.[35–40] Patients with primary cytogenetic resistance to first- and second-line therapy did not benefit from sequential therapy with second-generation TKIs.[38] There was little evidence of cross-intolerance,[35,39] but additional data are needed to discern which patients are most likely to benefit from a second-generation TKI in the third-line setting. Finally, the consistent failure of second-generation TKIs in T315I-positive patients[35,37,39] supports *BCR-ABL1* mutational analysis in all patients who develop TKI-resistant disease.

Third-Generation TKI

The third-generation TKI ponatinib was evaluated in the phase 2 PACE trial,[41] which enrolled 449 patients with CML or Ph+ ALL who were resistant or intolerant to dasatinib or nilotinib, or who had the T315I mutation. Nearly all of the patients (93%) had received 2 or more approved TKIs before receiving ponatinib, and only 12% of patients were intolerant to dasatinib or nilotinib. After a median follow-up of 15 months, MCyR, CCyR, and major molecular response (MMR) rates among the CP-CML subgroup analyzed for efficacy (n=267) were 56%, 46%, and 34%, respectively.[41] After a median follow-up of 28 months, MCyR, CCyR, and MMR rates among patients with CP-CML were 59%, 53%, and 38%, respectively, and 2-year progression-free survival (PFS) was estimated to be 67% (Table 2).[42]

A prospectively defined analysis of PACE,[43] conducted after a median follow-up of 12 months, evaluated the impact of previous TKI exposure on the efficacy of ponatinib in the CP-CML population. Patients receiving fewer prior approved TKIs had higher MCyR rates (1 vs 3 prior approved TKIs, 84% vs 46% [P=0.003]; 2 vs 3, 63% vs 46% [P=0.011]). MCyR rates among patients with the T315I mutation and 1, 2, and 3 prior approved TKIs (n=63) were 91%, 77%, and 52%, respectively. MMR rates did not vary significantly by degree of TKI pretreatment. These results are consistent with a multivariate analysis of PACE data,[44] which showed that higher MCyR rates among patients with T315I, compared with patients without T315I, were likely the result of higher dose intensity, younger age, and fewer prior TKIs. This evidence suggests that treating patients with ponatinib earlier in the course of the disease may lead to improved response rates. The higher response rates observed with ponatinib versus second-generation TKIs in heavily pretreated patients (Table 2) may be related to the lack of any single mutation conferring resistance to ponatinib in CP-CML to date. Furthermore, the activity of ponatinib was generally unaffected by baseline compound mutations (with or without T315I) among patients with CP-CML in the PACE trial, and few patients gained mutations during ponatinib treatment.[45,46] However, comparisons across TKI studies should be made with caution. Patient numbers were limited in most cases, and patient characteristics differed with respect to duration of disease and extent of prior non-TKI therapy. Prospective data from large, comparative studies in the third-line setting are needed. Updated US Food and Drug Administration labeling should also be considered when prescribing ponatinib. As of early 2014, ponatinib labeling included a revised warning regarding risk of vascular occlusions, heart failure, and hepatotoxicity; revised dosing information; and an indication limited to adults who are T315I-positive and adults for whom no other TKI is indicated.[26] Vascular events occurred in 24% of patients in the PACE trial, including younger patients, and in 48% of patients with CML or Ph+ ALL in the dose-escalation (phase 1) clinical trial.[26] ARIAD has initiated a Risk Evaluation and Mitigation Strategy program aiming to inform prescribers of the risk of vascular events associated with ponatinib and of the revised indications.

How Do We Identify Patients for Whom Second- or Third-Line Treatment With a Second-Generation TKI Is Not the Best Choice?

Evidence suggests that long-term PFS rates for second-generation TKIs in CP-CML patients resistant or intolerant to imatinib are modest (4-year PFS with nilotinib, 57%[47]; 6-year PFS with dasatinib, 49%[48]). Independent predictors of response and outcome with second-generation TKIs used in second- or third-line treatment have been identified.[49–55] Prior cytogenetic response is the most robust positive prognostic factor identified to date in patients with CML receiving second-generation TKIs after imatinib failure (Table 3).[49–51] Mutation analyses have also proven beneficial in predicting CML outcomes with TKIs following imatinib failure. Among CP-CML patients treated with dasatinib or nilotinib after imatinib failure, those with baseline *BCR-ABL1* mutations less sensitive to second-generation TKIs (eg, F317L [low sensitivity to dasatinib] and Y253H, E255K/V, and F359C/V [low sensitivity to nilotinib]) and those with T315I (refractory to all second-generation TKIs) had lower CCyR and PFS rates than those with baseline mutations sensitive to second-generation TKIs.[56–58] Similarly, rates of MCyR were low in CP-CML patients with F317L (1 of 7), E255K/V (0 of 2), and T315I (0 of 6) mutations who received bosutinib after failure of imatinib and nilotinib and/or dasatinib.[39] In an analysis of 47 patients with CML resistant to 1 or more TKIs (imatinib, dasatinib, nilotinib, or bosutinib) who received an HSCT and had *BCR-ABL1* sequencing, patients with mutations (n=19, 17 of which were in accelerated phase or blast phase) had significantly reduced 2-year event-free survival (EFS) and overall survival rates (36% and 44%, respectively) compared with patients without mutations (58% and 76%, respectively).[59] These findings support *BCR-ABL1* mutation screening for all patients at the time of TKI failure to detect mutations with low sensitivity to second-generation TKIs, particularly the T315I mutation and multiple mutations (eg, Y253H and F317L) that confer resistance to all second-generation TKIs.[60] High-sensitivity sequencing techniques (eg, next-generation sequencing) are particularly useful for detection of low-level mutations, including compound mutations, which may not be detected by direct sequencing.[11,45]

Consistent with the aforementioned studies, a multivariate approach applied to results of dasatinib clinical trials in CP-CML patients (N=1150) identified prior MCyR with imatinib and absence of the T315I mutation as independent favorable prognostic factors for MCyR with dasatinib.[61] The same analysis also identified younger age, lower percentage of Ph+ cells, imatinib intolerance (vs resistance), no prior HSCT, and shorter time from CML diagnosis to dasatinib therapy as independent positive prognostic factors for MCyR. These same baseline factors also independently predicted CCyR.[61]

The recognition of a number of factors as potentially useful predictors of outcomes with second-generation TKIs following imatinib failure has led to the development of prognostic scoring models that incorporate combinations of prognostic factors (Table 4).[50,52,53] For example, Jabbour and colleagues[50] in 2011 proposed a prognostic score based on 2 factors: lack of any cytogenetic response to imatinib and Eastern Cooperative Oncology Group performance status of 1 or greater at the start of second-generation TKI therapy post–imatinib failure. Patients with poor performance status and no previous cytogenetic response to imatinib had low probability of responding to second-generation TKIs and were expected to have a low rate of EFS; therefore, these patients should be offered alternative options.[50]

Alternatively, the Hammersmith score is based on 3 factors: best cytogenetic response to imatinib, Sokal risk score, and recurrent grade 3/4 neutropenia during imatinib treatment that required dose reduction to less than 400 mg/d despite hematopoietic growth factor support.[52] Patients with a low Hammersmith score are expected to benefit from dasatinib or nilotinib, whereas those with a high Hammersmith score may consider HSCT. Patients with an intermediate Hammersmith score could be treated with second-generation TKIs, and their cytogenetic response at 3 or 6 months could guide the decision to maintain or change therapy.[52] The predictive value of the Hammersmith score was recently validated in 137 CP-CML patients.[55] In a multivariate analysis, a low risk score was significantly associated with better overall survival (P=0.0062) but not failure-free survival (P=0.16). Based on logistic regression analysis, there was a significant relationship between the Hammersmith score and achievement of CCyR (P=0.0002) and MMR or better (P=0.0003).[55]

A more comprehensive prognostic scoring system, devised by the investigators of the pivotal phase 2 trial of nilotinib, was developed for use after 12 months of treatment with nilotinib.[53] This system includes 4 factors: baseline mutations with low sensitivity to nilotinib, baseline hemoglobin less than 120 g/L, baseline basophils 4% or greater, and lack of MCyR by 12 months.[53] A prognostic score that includes only the first 3 factors was also developed for use at baseline. Patients with a kinase domain mutation with low sensitivity to nilotinib, anemia, or a high proportion of basophils in peripheral blood had a 2-year PFS rate of 0% when treated with nilotinib.[53] Alternative options should be offered to these patients, and may include ponatinib, HSCT, omacetaxine mepesuccinate, or an investigational drug.[62,63]

The data used to develop these prognostic models were derived from patients treated with dasatinib or nilotinib following imatinib failure. However, the second-generation TKIs dasatinib and nilotinib are increasingly being used as first-line therapy, and no prognostic models have been developed for patients after failure of second-generation TKIs in the first-line setting. Because dasatinib and nilotinib are more potent than imatinib, patients who experience treatment failure with these second-generation TKIs may have a worse prognosis than patients who experience treatment failure with imatinib. Thus, when interpreting results of the prognostic models reviewed in this article, previous treatments and current line of therapy should be taken into account. Although these prognostic scoring systems may inform second- and third-line treatment decisions in patients with CP-CML, they require further evaluation in larger, real-world patient populations.

How Can Long-term Outcomes With Sequential TKI Use Be Assessed?

Individual CML therapies are typically assessed by reporting response rates, EFS, and overall survival. Because a CML patient who experiences treatment failure with one TKI may be rescued by another, methods that predict long-term outcomes with sequential therapies could be clinically useful. Al-Kali and colleagues[64] recommended the use of current event-free survival (CEFS) in this setting. Whereas conventional EFS reflects the expected outcome of a single, isolated intervention, CEFS takes into account response to subsequent interventions. In a study that applied the CEFS concept to sequential TKIs, the authors studied 281 CP-CML patients who received imatinib as first-line therapy, 41 of whom experienced an event (ie, no CCyR by 18 months, or loss of CCyR at any time).[64] Fourteen achieved and maintained CCyR with a second TKI and were considered rescued, thus reversing the previous event at the time the most recent CCyR was documented. The estimated 7-year conventional EFS for this group of patients was 81%, but the estimated 7-year CEFS was 88%.[64] CEFS estimates are greater than EFS estimates because patients with events may be rescued and returned to the at-risk pool. Although CEFS has not been reported for large, prospective clinical trials evaluating TKIs after prior TKI failure, the concept has been used to estimate long-term outcomes in CML patients who have undergone HSCT.[65] In these patients, relapses can be salvaged by donor lymphocyte infusion or repeat HSCT.

Recommendations for Treatment of CML Patients in Whom First- and/or Second-Generation TKIs Fail

TKI Selection in Sequential-Use Settings

Patients who experience TKI failure in the first-line setting should be assessed for second-line therapy, and second-generation TKIs (dasatinib, nilotinib, or bosutinib) may be offered with consideration of favorable prognostic factors, such as cytogenetic response to first-line therapy, good performance status, low Sokal risk score, sensitive *BCR-ABL1* mutations only, no recurrent neutropenia, lack of anemia, normal proportion of basophils in peripheral blood, and low disease burden. If treatment with a second-generation TKI is initiated, patients should be monitored closely for response, and those who are not responding should be switched to another therapy.

Patients who experience treatment failure with a second-generation TKI as first- or second-line therapy should be switched to a third-generation TKI, unless the patient is experiencing intolerance to a specific second-generation TKI or the patient has responded and then acquired a specific mutation that has sensitivity to another second-generation TKI. For example, bosutinib has a favorable toxicity profile with a low incidence of some adverse events common with other TKIs (eg, pleural effusion and cardiac toxicity), and it has activity against many BCR-ABL1 kinase domain mutations resistant to imatinib, dasatinib, and nilotinib, although not T315I.[39] Patients who develop rash while receiving nilotinib[20] or bosutinib[23] may not when switched to dasatinib.[17] Patients who experience pleural effusion while taking dasatinib[17] may not with nilotinib[20] or bosutinib[23] (Table 1). Regarding mutations, the F317L/V/I/C mutations are more sensitive to nilotinib or bosutinib than to dasatinib, while Y253F/H, E255K/V, and F359V/I/C mutations are more sensitive to dasatinib or bosutinib than to nilotinib, and the V299L mutation is more sensitive to nilotinib than to dasatinib or bosutinib.[10,57,58,66] The decision to switch to a third-generation TKI should be guided by careful consideration of the benefits and risks, and risk factors for potential adverse events should be managed appropriately. The cases described later in this article show how treatment response, tolerability, and compliance may be maximized in patients who experience first- or second-line treatment failure with second-generation TKIs, and they illustrate appropriate use of the third-generation TKI ponatinib in this patient population.

For patients who are not candidates for subsequent TKI therapy after the development of resistance or intolerance to at least 2 TKIs, omacetaxine mepesuccinate and investigational drugs should be considered. Omacetaxine is a protein synthesis inhibitor that reduces levels of multiple oncoproteins, including BCR-ABL1 and MCL1, to induce apoptosis in leukemic cells.[67,68] Among 81 CP-CML patients who developed resistance or intolerance to at least 2 TKIs, omacetaxine achieved or maintained (for ≥8 weeks) hematologic response in 56 (69%) patients and achieved MCyR in 16 (20%) patients, including CCyR in 8 (10%) patients.[69] The median duration of MCyR was 18 months. Hematologic toxicity was most common, and therefore patients receiving omacetaxine should be monitored closely.[69]

Role and Timing of Allogeneic HSCT

Although not the primary focus of this article, Table 5 provides the authors' recommendations concerning HSCT. In patients with advanced disease, outcomes with second- and third-generation TKIs are generally not satisfactory, although a substantial fraction of patients in accelerated phase and a minority of patients in blast phase can benefit from prolonged response to therapy.[41,70–73] HSCT is recommended for eligible patients. While a donor is being secured, these patients may receive TKIs. In patients with CP-CML after failure of imatinib or a second-generation TKI used in the first-line setting, HSCT should be reserved for those who have a low probability of response to second- and third-generation TKIs, such as patients with no cytogenetic response to imatinib or other TKIs and patients who harbor mutations with low sensitivity to second-generation TKIs.[59] Patients with the T315I mutation can also be considered for early HSCT, and may be treated with ponatinib, the only TKI indicated for T315I-positive patients, while a donor is secured. If a patient has achieved an MCyR and maintained the response for 12 months or longer, one could put HSCT on hold. HSCT may represent a third- or fourth-line option in patients with CP-CML after TKI failure in the first-line setting if there was a good initial response to imatinib and if no mutations have been detected. These patients can receive long-term treatment with a TKI as second-line therapy. Elderly patients in whom imatinib therapy has failed may also receive long-term treatment with a TKI in the second-line setting, because quality of life is a priority for these patients.

Case Studies

Case 1

A 52-year-old man was diagnosed with CP-CML in September 2007, with a white blood cell count of 157,000/μL, 40% hematocrit, and a platelet count of 387,000/μL. Sokal risk score was intermediate. Cytogenetic analysis revealed that 20/20 metaphase cells were Ph+, with no additional abnormalities. Quantitative polymerase chain reaction (PCR) indicated a *BCR-ABL1/ABL1* ratio of 76% on the International Scale. This patient had a past medical history of significant drug and alcohol use. Treatment with imatinib 400 mg daily was initiated. The patient experienced nausea and vomiting while taking imatinib, and, within 3 weeks of initiating therapy, he developed an erythematous rash covering 80% of his body, requiring treatment with prednisone. In February 2008, the patient stopped taking imatinib and switched to dasatinib 100 mg daily.

While taking dasatinib, the patient experienced diarrhea characterized by 4 to 5 watery stools 3 to 4 days per week, facial acne, and nausea and epigastric pain 3 to 4 times per week, requiring periodic treatment with prochlorperazine. The compliance of the patient in regard to taking dasatinib was not entirely certain. The duration of adverse events was not fully documented, as the patient did not go to regular visits. The *BCR-ABL1* transcript ratio was drastically reduced to 0.01% 6 months after initiation of dasatinib (August 2008). In July 2009, the *BCR-ABL1* transcript ratio was 0.41%; in January 2010 it increased to 6.8%; in September 2010 it further increased to 10.5%; and in January 2011 it plateaued at 11%. Bone marrow examinations were conducted in September 2010 and January 2011, with 7/20 and 8/20 Ph+ metaphase cells, respectively. Mutation testing was performed and no mutations were detected.

As the patient was deemed not an HSCT candidate due to social and financial issues, the patient started receiving ponatinib 45 mg daily in February 2011. While taking ponatinib, the patient experienced nausea and epigastric pain 3 to 4 times per week (an adverse event very similar to that experienced while on dasatinib) and, after 15 days of ponatinib therapy, the patient developed an erythematous rash affecting more than 45% of his body. After a 2-week break from ponatinib therapy, the patient started taking ponatinib again but at a lower dose (30 mg daily). While on ponatinib, the patient achieved CCyR, as well as a deep molecular response (*BCR-ABL1* transcript ratio of 0.05%) at 3 months. The deep molecular response was maintained at 6 and 9 months (*BCR-ABL1* transcript ratio of 0.01% at both time points), and at 18 months *BCR-ABL1* transcripts were undetectable by PCR. Since *BCR-ABL1* transcripts remained undetectable for more than 1 year, the patient's dose was reduced to 15 mg daily in October 2013 (at 34 months). At the following molecular analysis in February 2014 (at 38 months), *BCR-ABL1* transcripts were still undetectable.

Case 2

A 35-year-old man was diagnosed with CP-CML in October 2009 following a regular check-up. Sokal risk score was low. The patient had no significant comorbidities or medical history and was not receiving any medications at the time of diagnosis. Treatment was initiated with dasatinib 100 mg daily. This therapy was well tolerated by the patient. At 3 months, *BCR-ABL1* transcript ratio was 5%, indicating an optimal response (≤10% [International Scale] or partial cytogenetic response by 3 months[62]) to dasatinib. The patient continued to receive dasatinib, and treatment was well tolerated with minor supportive interventions. At 6 months, quantitative PCR showed a *BCR-ABL1* transcript ratio of 2% and at 12 months the ratio dropped to 1%, which is considered approximately equivalent to CCyR, an optimal response.[62] At 18 months, molecular response improved to a *BCR-ABL1* transcript ratio of 0.5%. Subsequently, at 36, 48, and 54 months, *BCR-ABL1* was undetectable.

Case 3

A 71-year-old man presented with fatigue in 2008 and was diagnosed with CP-CML. Sokal risk score was high. The patient had a prior medical history of mild hypertension and was taking a statin. The patient started treatment with dasatinib 100 mg daily as part of the DASISION (Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients) trial and achieved MMR by 12 months. In March 2013, the patient reported increased fatigue and weight loss and *BCR-ABL1* transcript analysis revealed a 1.5-log increase in the *BCR-ABL1* transcript ratio. In April 2013, a bone marrow biopsy revealed 80% cellularity, 1%

blasts, and no evidence of dyspoiesis. Mutation testing demonstrated the presence of the T315I mutation, cytogenetic analysis showed 15/20 Ph+ metaphases, and complete blood cell count was normal.

As a result, dasatinib therapy was discontinued and the patient began treatment with ponatinib 45 mg daily. While receiving ponatinib, the patient experienced recurrent episodes of grade 3 thrombocytopenia. Therefore, the ponatinib dose was reduced to 30 mg daily in May 2013. In July 2013, cytogenetic analysis showed 10% Ph+ metaphases and *BCR-ABL1* transcript analysis revealed a ratio of 4.28%. The patient achieved CCyR in October 2013, when his *BCR-ABL1* transcript ratio was 0.85%. The patient maintained a deep molecular response in March 2014 when his *BCR-ABL1* transcript ratio was 0.01% and no mutation was detected.

Conclusion

Tyrosine kinase inhibition revolutionized CML management, and the availability of 5 different TKIs indicated for CML provides patients and physicians with a range of alternatives following TKI failure. The data reviewed here suggest that independent prognostic factors and multifactor models may be helpful for identification of patients who are unlikely to achieve deep, durable responses to a second-generation TKI after failure of imatinib or a prior second-generation TKI. Ponatinib, HSCT, omacetaxine, and investigational therapies are important options to consider for these patients. The current literature also suggests that the use of a second-generation TKI as third-line therapy is of limited value in most CML patients.

Unique toxicities are associated with the different TKIs used for the treatment of CML, including: edema and fluid retention (imatinib); pleural effusion, bleeding, and pulmonary hypertension (dasatinib); bilirubin, lipase, and glucose elevations and peripheral arterial events (nilotinib); diarrhea, rash, and transaminase elevation (bosutinib); and vascular occlusion and heart failure (ponatinib). Therefore, certain TKIs may be more or less appropriate for specific patients. Risk factors should be managed, where possible, and treatment decisions should reflect the expected benefits and risks of the various options.

Future research should aim to identify additional prognostic tools that may help optimize subsequent CML therapy in the setting of TKI failure, and to broaden our understanding of the mechanisms underpinning TKI resistance. These efforts may further advance the individualization of CML care and ultimately lead to improved outcomes.

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Table 1

...ed for the Treatment of CML

...nding to ...BL1	Other Kinases Inhibited	Primary Route of Metabolism	Elimination Half-Life	Drug Interactions	Dosing With Food	Ph+ CML/ALL Indications: United States	Ph+ CML/ALL Indications: European Union	Unique Toxicities
...n TKI								
...active conformation[13]	• PDGFR • KIT[14]	CYP3A4[14]	• Parent: 18 h • Major active metabolite: 40 h[14]	• CYP3A4 inducers may decrease and CYP3A4 inhibitors may increase C_{max} and AUC of imatinib • Imatinib is an inhibitor of CYP3A4 and CYP2D6, which may increase C_{max} and AUC of other drugs • Patients who need anticoagulation should receive low-molecular-weight or standard heparin, not warfarin[14]	Take with food[14]	• Newly diagnosed adult and pediatric patients with Ph+ CP-CML • Patients with Ph+ CP-, AP-, or BP-CML after failure of interferon alfa therapy • Adult patients with relapsed or refractory Ph + ALL • Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy[14]	• Newly diagnosed adult and pediatric patients with Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment • Adult and pediatric patients with Ph+ CP-CML after failure of interferon alfa therapy, or AP- or BP-CML • Adult patients with relapsed or refractory Ph + ALL • Adult and pediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy[15]	Edema, fluid retention[14]
...tion TKIs								
...ultiple conformations[16]	• SRC family (SRC, LCK, YES1, FYN) • KIT	CYP3A4[17]	3–5 h[17]	• CYP3A4 inhibitors may increase drug levels and should be avoided; if coadministration cannot be	Take with or without food[17]	• Newly diagnosed adults with Ph+ CP-CML • Adults with Ph + CP-, AP-, or BP-CML with	• Newly diagnosed adults with Ph+ CP-CML • Adults with CP-, AP-, or BP-CML with	Pleural effusion, bleeding, pulmonary hypertension[17]

...nding to ...BL1	Other Kinases Inhibited	Primary Route of Metabolism	Elimination Half-Life	Drug Interactions	Dosing With Food	Ph+ CML/ALL Indications: United States	Ph+ CML/ALL Indications: European Union	Unique Toxicities
	• EPHA2 • PDGFRB[17]			avoided, monitor closely and consider reducing dasatinib dose • CYP3A4 inducers may decrease drug levels; if coadministration cannot be avoided, consider increasing dasatinib dose • Antacids may decrease drug levels; if needed, administer antacid ≥ 2 h before or ≥ 2 h after dasatinib dosing • H_2 antagonists/ proton pump inhibitors may decrease drug levels; consider antacids instead[17]		resistance or intolerance to prior therapy including imatinib • Adults with Ph + ALL with resistance or intolerance to prior therapy[17]	resistance or intolerance to prior therapy including imatinib • Adults with Ph + ALL or lymphoid BP-CML with resistance or intolerance to prior therapy[18]	
...ctive conformation[19]	• PDGFR • KIT • CSF1R • DDR1[20]	CYP3A4[20]	17 h[20]	• Nilotinib may alter serum concentration of other drugs • CYP3A4 inhibitors and inducers may affect serum concentration of nilotinib[20]	Avoid food ≥ 2 h before and ≥ 1 h after the dose is taken[20]	• Newly diagnosed adults with Ph+ CP-CML • Adults with Ph + CP- or AP-CML with resistance or intolerance to prior therapy that included imatinib[20]	• Newly diagnosed adults with Ph+ CP-CML • Adults with Ph + CP- or AP-CML with resistance or intolerance to prior therapy including imatinib[21]	Bilirubin, lipase, glucose elevations, peripheral arterial events[20]
...ultiple conformations[22]	• SRC family (SRC,	CYP3A4[23]	22.5 h[23]	• Avoid concurrent use of bosutinib	Take with food[23]	• Adults with Ph + CP-, AP-, or BP-CML with	• Adults with Ph + CP-, AP-, or BP-CML	Diarrhea, rash, transaminase elevation[23]

...nding to ...BL1	Other Kinases Inhibited	Primary Route of Metabolism	Elimination Half-Life	Drug Interactions	Dosing With Food	Ph+ CML/ALL Indications: United States	Ph+ CML/ALL Indications: European Union	Unique Toxicities
	LYN, HCK)[23]			with strong or moderate CYP3A inhibitors and inducers • Proton pump inhibitors may decrease drug levels; consider short-acting antacids instead[23]		resistance or intolerance to prior therapy[23]	previously treated with 1 or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate options[24]	
...on TKI								
...ctive conformation[25]	• VEGFR family • PDGFR family • FGFR family • EPH receptors • SRC family • KIT • RET • TEK (TIE2) • FLT3[26]	Esterases, amidases, CYP3A4[26]	24 h[26]	• Avoid concurrent use of strong CYP3A inhibitors; if coadministration cannot be avoided, reduce ponatinib dose • Avoid concurrent use of strong CYP3A inducers[26]	Take with or without food[26]	• Adults with T315I-positive CP-, AP-, or BP-CML • Adults with T315I-positive Ph+ ALL • Adults with CP-, AP-, or BP-CML or Ph + ALL for whom no other TKI is indicated[26]	• Adults with CP-, AP-, or BP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation • Adults with Ph + ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation[27]	Vascular occlusion, heart failure[26]

Abbreviations: ALL = acute lymphoblastic leukemia; AP = accelerated phase; AUC = area under the plasma concentration–time curve; BP = blast phase; C_{max} = maximum plasma concentration; CML = chronic myeloid leukemia; CP = chronic phase; CSF1R = colony stimulating factor 1 receptor; DDR1 = discoidin domain receptor tyrosine kinase 1; EPH = ephrin; EPHA2 = EPH receptor A2; FGFR = fibroblast growth factor receptor; PDGFR = platelet-derived growth factor receptor; PDGFRB = platelet-derived growth factor receptor, beta polypeptide; Ph+ = Philadelphia chromosome–positive; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Table 2

Studies Evaluating Use of Specific Second- or Third-Generation TKIs in the Third-Line Setting and Beyond

Reference	Patient Population (Disease State at Start of Study Drug)	Prior TKI(s)	Treatment (Starting Dose Used in Study) and Setting	Duration of Follow-up (Since Start of Study Drug)	Key Efficacy Outcomes
Second-Generation TKIs					
Garg et al 2009[35]	CML (N=48) CP-CML (n=25) AP-CML (n=10) BP-CML (n=13)	Imatinib → nilotinib (n=34) Imatinib → dasatinib (n=14)	Dasatinib (50–140 mg qd or 50–120 mg bid; n=34) or nilotinib (400–800 mg qd or 400 mg bid; n=14) in third-line setting	Median, 13 mo (range, 0.5–41)	CHR: 76%, CP; 90%, AP; 46%,[a] BP MCyR[b]: 40%, CP; 40%, AP; 31%, BP CCyR[b]: 32%, CP; 20%, AP; 23%, BP MMR: 20%, CP; 10%, AP; 8%, BP Median EFS: 13 mo Median FFS: 5 mo (20 mo, CP; 5 mo, AP; 3 mo, BP) Median OS: 20 mo
Nicolini et al 2009[36]	CML (N=292) CP-CML (n=218) AP-CML (n=34) BP-CML (n=40)	Imatinib → dasatinib (n=292)	Nilotinib (400 mg bid) in third-line setting	Not reported; median exposure, 7 mo (range, 0.1–25)	CHR: 40%, CP; 10%, AP; 3%, BP MCyR: 41%, CP; 7%, AP; 14%, BP CCyR: 28%, CP
Giles et al 2010[37]	CML (N=54) CP-CML (n=37) AP-CML (n=17)	Imatinib → dasatinib (n=54)	Nilotinib (400 mg bid) in third-line setting	Median, 12 mo	CHR: 79%,[c] CP; 29%, AP MCyR: 43%, CP; 12%, AP CCyR: 24%, CP; 0%, AP 18-mo PFS: 59%, CP 18-mo OS: 86%, CP
Ibrahim et al 2010[38]	CP-CML (N=26)	Imatinib → nilotinib (n=6) Imatinib → dasatinib (n=20)	Dasatinib (standard doses; n=6) or nilotinib (standard doses; n=20) in third-line setting	Median, 22 mo (range, 6–47)	MCyR: 50% CCyR: 35% MMR: 19% 30-mo EFS: 46% 30-mo OS: 47%
Khoury et al 2012[39]	CP-CML (N=118)	Imatinib → nilotinib (n=28) Imatinib → dasatinib (n=87) Imatinib → dasatinib → nilotinib (or imatinib → nilotinib → dasatinib) (n=3)	Bosutinib (500 mg qd) in third-line setting (n=115) or fourth-line setting (n=3)	Median, 29 mo (range, 0.3–56)	CHR: 65%[d] MCyR: 32% CCyR: 24% MMR: 15% 1-y PFS: 77% 2-y PFS: 73% 1-y OS: 91% 2-y OS: 83%
Russo Rossi et al 2013[40]	CML (N=82) CP-CML (n=68) AP-CML (n=9) BP-CML (n=5)	Imatinib → nilotinib (n=34) Imatinib → dasatinib (n=48)	Dasatinib (dose not specified; n=34) or nilotinib (dose not specified; n=48) in third-line setting	Median, 14 mo (range, 2–37)	CHR: 85% MCyR: 48%[b] CCyR: 33%[b] MMR: 16%

Reference	Patient Population (Disease State at Start of Study Drug)	Prior TKI(s)	Treatment (Starting Dose Used in Study) and Setting	Duration of Follow-up (Since Start of Study Drug)	Key Efficacy Outcomes
Third-Generation TKI					
Cortes et al 2013[41] Cortes et al 2014[42]	CML or Ph+ ALL (N=449) CP-CML (n=270) AP-CML (n=85) BP-CML (n=62) Ph+ ALL (n=32)	93% received ≥2 prior approved TKIs (imatinib, dasatinib, nilotinib, or bosutinib); 55% received ≥3; 444 were resistant or intolerant to dasatinib or nilotinib, or had the T315I mutation[e]	Ponatinib (45 mg qd) in second-, third-, fourth-, or fifth-line setting (considering prior approved TKIs only)	Median, 28 mo (range, 0.1–40)	CP-CML[e]: MCyR: 59% CCyR: 53% MMR: 38% 2-y PFS: 67% 2-y OS: 86% AP-CML[e]: MaHR: 61% 2-y OS: 72% BP-CML: MaHR: 31% 2-y OS: 18% Ph+ ALL: MaHR: 41% 2-y OS: 18%

Abbreviations: ALL = acute lymphoblastic leukemia; AP = accelerated phase; bid = twice daily; BP = blast phase; CCyR = complete cytogenetic response; CHR = complete hematologic response; CML = chronic myeloid leukemia; CP = chronic phase; EFS = event-free survival; FFS = failure-free survival; MaHR = major hematologic response; MCyR = major cytogenetic response; MMR = major molecular response; OS = overall survival; PFS = progression-free survival; Ph+ = Philadelphia chromosome–positive; qd = once daily; TKI = tyrosine kinase inhibitor.

[a]Rate includes return to CP.

[b]Study reported best responses; lesser responses are included.

[c]Rate is among 28 patients without CHR at baseline.

[d]Rate is among 68 patients without CHR at baseline.

[e]Five patients with a history of the T315I mutation but no T315I mutation detected at baseline (3 CP-CML; 2 AP-CML) were excluded from the efficacy population.

Table 3

Cytogenetic Response as an Independent Predictor of Clinical Outcomes in CML Patients Receiving TKIs Post–Imatinib Failure

Reference	Patient Population	TKI Therapy	Predictive Factor (Time Frame)	Outcomes	
				EFS	**OS**
Tam et al 2008[49]	N=113 CP-CML (n=87) AP-CML (n=26)	Nilotinib (n=43) or dasatinib (n=70)	MCyR vs MiCyR or CHR (by 1 y)	At 2 y: probability of progression 3% (with 1-y MCyR) vs 17% (with 1-y MiCyR or CHR), P=0.003	At 2 y: 97% (with 1-y MCyR) vs 84% (with 1-y MiCyR or CHR), P=0.02
Jabbour et al 2011[50]	CP-CML (N=123)	Nilotinib (n=45) or dasatinib (n=78)	MCyR vs no MCyR (at 1 y)	After median follow-up of 38 mo: lack of 1-y MCyR adverse factor for EFS; HR=2.3, P<0.001	NR
Jabbour et al 2013[51]	CP-CML (N=123)	Nilotinib (n=45) or dasatinib (n=78)	CCyR vs no CCyR (at 3 mo)	At 3 y: 74% (with 3-mo CCyR) vs 43% (without 3-mo CCyR), P=0.002; multivariate analysis: HR=4.5 (95% CI, 2.12–11.66), P<0.01	At 3 y: 98% (with 3-mo CCyR) vs 79% (without 3-mo CCyR), P=0.005; multivariate analysis: HR=5.4 (95% CI, 1.27–10.87), P=0.03

Abbreviations: AP = accelerated phase; CCyR = complete cytogenetic response; CHR = complete hematologic response; CI = confidence interval; CML = chronic myeloid leukemia; CP = chronic phase; EFS = event-free survival; HR = hazard ratio; MCyR = major cytogenetic response; MiCyR = minor cytogenetic response; NR = not reported; OS = overall survival; TKI = tyrosine kinase inhibitor.

Table 4

Predictive Models for Outcome With TKI Therapy in Patients With CP-CML Post–Imatinib Failure

Reference	Patient Population	TKI Therapy	Factors Included in Scoring	Risk Groups	Discrimination of Outcomes Using Prognostic Models			
					EFS	PFS	OS	CyR
Jabbour et al 2011[50]	CP-CML (N=123)	Nilotinib (n=45) or dasatinib (n=78)	• Lack of any cytogenetic response to imatinib • ECOG PS ≥1 at start of second-generation TKI therapy post–imatinib failure	• Low risk = 0 risk factors (n=59) • Intermediate risk = 1 risk factor (n=48) • High risk = 2 risk factors (n=5)	2-Year: • Low risk, 78% • Intermediate risk, 49% • High risk, 20% *P*<0.001	NR	2-Year: • Low risk, 95% • Intermediate risk, 85% • High risk, 40% *P*=0.002	1-Year MCyR: • Low risk, 64% • Intermediate risk, 36% • High risk, 20% *P*=0.007
Milojkovic et al 2010[52]	CP-CML (N=80)	Nilotinib (n=13) or dasatinib (n=67)	• Best cytogenetic response to imatinib (CCyR, 0 points; 1%–94% Ph + metaphases, 1 point; ≥95% Ph+ metaphases, 3 points) • Sokal risk score (low, 0 points; intermediate or high, 0.5 points) • Neutropenia on imatinib (none, 0 points; recurrent grade 3/4 neutropenia requiring dose reduction to <400 mg/d, 1 point)	• Low risk = total score <1.5 (n=24) • Intermediate risk = total score 1.5–2.5 (n=27) • High risk = total score >2.5 (n=29)	2.5-Year: • Low risk, NR • Intermediate risk, 72.1% • High risk, NR	2.5-Year: • Low risk, 100% • Intermediate risk, 89.3% • High risk, 77.6% *P*=0.02 for low vs high risk	2.5-Year: • Low risk, 100% • Intermediate risk, 90.7% • High risk, 89.9% *P*=0.02 for low vs high risk	2.5-Year cumulative incidence of CCyR • Low risk, 100% • Intermediate risk, 52.2% • High risk, 13.8% *P*<0.0001
Jabbour et al 2013[53]	CP-CML (N=321)	Nilotinib	**Overall score** • Baseline mutations with low sensitivity to nilotinib • Baseline Hb <120 g/L • Baseline basophils ≥4% • Lack of MCyR by 12 mo	Score 0 = 0 risk factors (n=77) Score 1 = 1 risk factor (n=116) Score 2 = 2 risk factors (n=82) Score 3 = 3 risk factors (n=31) Score 4 = 4 risk factors (n=9)	2-Year: • 0, 81% • 1, 50% • 2, 29% • 3, 8% • 4, 0% *P*<0.001	2-Year: • 0, 89% • 1, 67% • 2, 50% • 3, 19% • 4, 0%	2-Year: • 0, 99% • 1, 88% • 2, 76% • 3, 82% • 4, 87% *P* <0.001 for score 0 vs scores 1, 2, 3, or 4	NR
			Baseline score • Baseline mutations with low sensitivity to nilotinib • Baseline Hb <120 g/L • Baseline basophils ≥4%	Score 0 = 0 risk factors (n=109) Score 1 = 1 risk factor (n=153) Score 2 = 2 risk factors (n=41) Score 3 = 3 risk factors (n=12)	NR	2-Year: • 0, 79% • 1, 65% • 2, 39% • 3, 0%	2-Year: • 0, 93% • 1, 84% • 2, 81% • 3, 90% *P* =0.06 for score 0 vs scores 1, 2, or 3	1-Year MCyR: • 0, 71% • 1, 55% • 2, 32% • 3, 25% *P* <0.001

Abbreviations: CCyR = complete cytogenetic response; CP-CML = chronic myeloid leukemia in chronic phase; CyR = cytogenetic response; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; Hb = hemoglobin; MCyR = major cytogenetic response; NR = not reported; OS = overall survival; PFS = progression-free survival; Ph+ = Philadelphia chromosome–positive; TKI = tyrosine kinase inhibitor.

Table 5

Recommendations for Role and Timing of Allogeneic HSCT in CML

Status	TKIs	Allogeneic HSCT
AP, BP	Interim treatment to MRD	If in remission
Imatinib or first-line second-generation TKI failure in CP, with T315I mutation	Ponatinib	If not responding well to ponatinib
Imatinib or first-line second-generation TKI failure in CP, no clonal evolution, no mutations, good initial response to imatinib	Long-term treatment with TKI in second-line setting	Third-line, post–second TKI failure
Imatinib or first-line second-generation TKI failure in CP, with clonal evolution, with mutations resistant to second-generation TKIs, no CyR to imatinib	Interim treatment with ponatinib eventually to MRD	As soon as possible if no response to ponatinib
Elderly patients, age >70 y, post–imatinib failure	Long-term treatment with TKI in second-line setting	Forego allogeneic HSCT for many years (maximize quality of life)

Abbreviations: AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase; CyR = cytogenetic response; HSCT = hematopoietic stem cell transplantation; MRD = minimal residual disease; TKI = tyrosine kinase inhibitor.