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CHRONIC MYELOID LEUKEMIA

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VIRTUAL WORKSHOP

SCIENTIFIC INTERCHANGE & WORKSHOP

KEY TAKEAWAY POINTS

- ▶ Multiple BCR-ABL1 tyrosine kinase inhibitors (TKIs) are available for effective treatment of chronic myeloid leukemia.
- ▶ The perception of the safety of TKIs and managing adverse events associated with their use remain ongoing challenges.
- ▶ Broad education on the proper use of these agents needs to be implemented.
- ▶ Treatment in the relapsed/refractory setting can be challenging, so choosing the right therapy to maximize clinical benefit is important.

Current and Future Trends in Chronic Myeloid Leukemia

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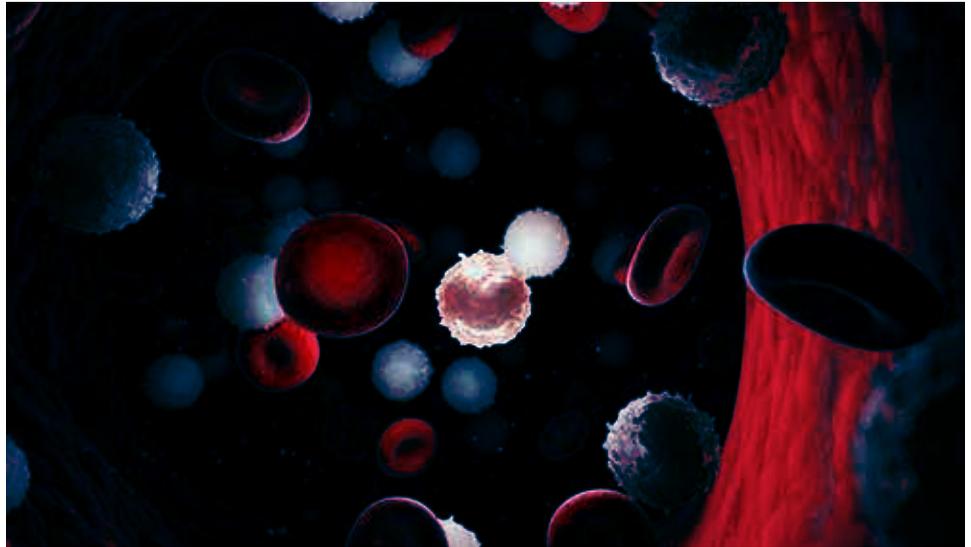
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Chronic Myeloid Leukemia



Current and Future Trends in Chronic Myeloid Leukemia

CHRONIC MYELOID LEUKEMIA (CML) is characterized by the presence of the abnormal *BCR-ABL1* oncogene, which develops from the translocation of t(9;22)(q34;q11) and encodes the BCR-ABL1 protein that has constitutive kinase activity.¹ CML has a 5-year relative survival rate of 70.4%, according to 2010-2016 data from the Surveillance, Epidemiology, and End Results Program.²

Although multiple BCR-ABL1 tyrosine kinase inhibitors (TKIs) offer effective treatment for CML,³ managing adverse events (AEs) and improving the perception of their safety remain ongoing challenges, according to oncologists who participated in a recent virtual *OncoLive® Scientific Interchange* workshop moderated by **Jorge Cortes, MD**, of Georgia Cancer Center in Augusta.

CML TREATMENT LANDSCAPE

At present, 5 TKIs, spanning 3 generations, are approved to treat chronic phase (CP) CML.^{4,5} Clinical considerations in the selection of TKI treatment focus on patient adherence, mutational *BCR-ABL* kinase domain status, potential drug interactions, treatment tolerance or resistance, known AEs of treatment, and a patient's comorbidities.^{3,5}

Imatinib, the only first-generation TKI, is commonly given as the first-line treatment option for patients with CML.⁴ Nilotinib, dasatinib, and bosutinib are second-generation TKIs approved for use in patients with CML who are resistant to or have failed treatment with imatinib.⁵ Currently, no standardized protocol is in place for patients who fail a second-generation TKI; however, a common practice is to switch to another second-generation TKI after failure or tolerance.⁴

Ponatinib, a third-generation TKI, is indicated by the FDA for the treatment of adult patients with (1) CP-CML with resistance or intolerance to at least 2 prior kinase inhibitors; (2) accelerated or blast phase CML or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) for whom no other kinase inhibitors are indicated; and (3) *T315I*-positive CML (CP, accelerated phase, or blast phase) or *T315I*-positive Ph+ ALL.⁶

It is crucial for physicians caring for patients with CML to be aware of which TKIs are available for each particular clinical situation, what can be expected from them, and how



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to manage their potential AEs. Common AEs associated with use of TKIs for treatment of CML include cytopenia, nausea, diarrhea, fatigue, rash, and liver damage. These can be managed with dose reductions or treatment suspensions.⁵

TKI TOLERABILITY IN SPECIFIC POPULATIONS

BCR-ABL1 TKIs are considered standard therapy for CML and are effective and generally well tolerated,³ although thrombocytopenia may require treatment interruptions and dose reductions, which may lead to loss of response, according to **Cortes**. Eltrombopag, a second-generation nonpeptide thrombopoietin receptor agonist, has demonstrated reductions in thrombocytopenia by positively affecting complete platelet and cytogenetic responses in patients with CML.⁷ **Cortes** noted that although it appears to be effective, eltrombopag is not yet approved for patients with CML and TKI-induced thrombocytopenia, and long-term data in a large group of patients are needed to confirm these findings.

The panelists discussed treatment options for patients who received a diagnosis of CML and renal insufficiency. **Kendra Sweet, MD, MS**, of the Moffitt Cancer Center in Tampa, Florida, and **Gabriela Hobbs, MD**, of Harvard Medical School and Leukemia Service at Massachusetts General Hospital in Boston, said that they prefer a second-generation TKI for young, high-risk patients, although **Hobbs** cautioned that evaluation of renal dysfunction is important before choosing a drug to reduce risk for fluid imbalance associated with progressive renal disease. **B. Douglas Smith, MD**, of Johns Hopkins University School of Medicine in Baltimore, Maryland, added that optimal dosing and treatment of patients with renal dysfunction can be a challenge because patients often lose some renal function naturally after several years of TKI use.

MONITORING PATIENTS DURING THERAPY

The panelists remarked that the use of TKIs and the monitoring of patients in the community setting is often suboptimal. A major contributor to efficacy and treatment response is adherence to treatment. **M. Yair Levy, MD**, of the US Oncology Network in Dallas, Texas, shared that he first assesses patient adherence because, in his experience, poor adherence is the most common cause of a suboptimal response. **Ellin Berman, MD**, of Memorial Sloan Kettering Cancer Center in New York, New York, added that she also checks to see if the patient is taking anything, such as an herbal preparation, that may interfere with absorption of the TKI.

CONSIDERATIONS FOR SWITCHING OF TKIs

Most of the panelists shared that because switching to another second-generation TKI is often ineffective, it may prove more beneficial to switch patients to a TKI of another generation entirely. However, **Michael Mauro, MD**, also of Memorial Sloan Kettering Cancer Center, said that he may consider switching to another second-generation TKI based on the rate of decrease in *BCR-ABL1* polymerase chain reaction (PCR) values over the 6-month period and whether there is room to modify the dose, but he emphasized that waiting too long could lead to development of higher-level resistance.

Jerald Radich, MD, of the Fred Hutchinson Cancer Research Center in Seattle, Washington, stated that his practice is often referred patients who have had their TKIs switched frequently, often on a monthly basis, because of AEs. A month, he noted, is not long enough to adequately assess for response. **Hobbs** added that setting treatment expectations around TKI-related toxicities may reduce premature switching of TKIs. **Ehab Atallah, MD**, of the Medical College of Wisconsin in Milwaukee, agreed, but he stressed that community practitioners should be particularly cautious about keeping a patient on a TKI that is severely affecting the patient's quality of life. He stated that he had observed patients experiencing extreme AEs for extended amounts of time before being switched to a different TKI.

Sweet said that in her experience, most patients treated in community practices are started on a second-generation TKI, most often dasatinib or nilotinib, although the rationale for the frontline choice is unclear. **Atallah** added that patient monitoring (in terms of the tests chosen) and management (based on abnormal test findings) are often inconsistent and inappropriate.

CLINICAL MANAGEMENT ASSESSMENTS IN CML

National Comprehensive Cancer Network guidelines recommend performing quantitative PCR analysis of *BCR-ABL1* gene expression using the International Scale every 3 months for patients with CML who are receiving TKI therapy, followed by bone marrow cytogenetics and mutation analysis of the *BCR-ABL1* kinase domain in patients who do not reach response milestones. For *BCR-ABL1* PCR results greater than 10% (indicating possible TKI resistance), the evaluation of patient compliance and drug interactions is recommended, as well as consideration of mutational analysis and bone marrow cytogenetic analysis. Management options in this situation include switching to an alternative TKI, continuing treatment with the same TKI, increasing the dose of imatinib (in some cases), and considering evaluation for allogeneic hematopoietic stem cell transplantation.³ »

Moshe Talpaz, MD, of the University of Michigan, Michigan Medicine, in Ann Arbor, said that he would likely switch to another second-generation TKI for intolerance in a young patient diagnosed with CP-CML if they had stage III renal insufficiency (glomerular filtration rate of 47 mL/min or less), an elevated white blood cell count, a high Sokal score, and a *BCR-ABL1* PCR of 20% at 3 months. He cautioned, however, that he would not necessarily switch TKIs in every patient with possible resistance.

Several of the panelists explained that they would choose ponatinib for the aforementioned patient in whom the high-risk presentation of CP-CML and a *BCR-ABL1* PCR greater than 10% remained after 6 months of continued treatment with a second-generation TKI. **Talpaz** said, “The high risk of disease and the lack of an adequate response to the currently prescribed second-generation TKI (noted as a *BCR-ABL1* > 10%) provide rationale for a switch to another TKI treatment.”

“This is a young patient with clearly resistant disease,” said **Sweet**. “To me, this is where...ponatinib is indicated. This is someone who I think probably has a very good chance of responding [to it].”

Radich added that in consideration of the patient’s renal dysfunction, he would start a myeloablative donor search in conjunction with starting ponatinib and would consider a nonmyeloablative transplantation if the patient did not respond in 3 to 6 months.

CONSIDERATIONS WITH SELECTION OF THERAPY

Although the panelists tended to prefer second-generation TKIs due to their efficacy, each of these agents has a different toxicity profile. Therefore, one second-generation TKI may be more suitable than another for a given patient.³ For example, the 10-year follow-up data from the ENESTnd trial (NCT00471497) of patients with CP-CML showed higher rates of cumulative major molecular response (MMR) at 10 years with 300-mg and 400-mg twice-daily doses of nilotinib compared with 400 mg of imatinib (82.6%, 80.4%, and 69.6%, respectively).⁸ However, the 300-mg and 400-mg doses of nilotinib, compared with imatinib, showed higher rates of AEs leading to discontinuation of study treatment (24.0%, 35.4%, and 20.0%, respectively), serious AEs (40.1%, 45.8%, and 34.6%, respectively), and exposure-adjusted overall incidence of cardiovascular (CV) events (0.30, 0.38, and 0.08 incidents per 10 patient-years, respectively). Results of the analysis also showed that the rates of CV events for each agent during the first 5 years of study treatment were similar to the rates after 5 years, indicating that CV-related risks associated with second-generation TKIs continue long term.⁸

The results of a meta-analysis of 14 randomized controlled trials that compared second-generation TKIs with imatinib or high-dose imatinib found that the rates of MMR and major cytogenetic response (MCyR) favored second-generation TKIs. However, the overall survival outcomes were not significantly improved (odds ratio, 1.17; 95% CI, 0.91-1.52). The incidence of arterial occlusive events (AOEs) was higher with the second-generation TKIs, with an estimated incidence rate of 61 per 1000 patients (95% CI, 46-79) vs 23 per 1000 patients with imatinib.⁹

To analyze a wider spectrum of AEs from a population of patients who may not have been included in clinical trials, a case/noncase study evaluated reports of AEs registered in the FDA Adverse Event Reporting System (FAERS) database to compare CV event reports among the TKIs approved for CML. According to the study authors, FAERS and similar spontaneous reporting systems allow quick analysis of the long-term risk-benefit profiles of drugs, help identify trends and associations with use, and facilitate the safe prescribing of drugs, making the systems a valuable resource for clinicians, regulators, and pharmaceutical companies. In the analysis, crude and adjusted (for age and sex) relative odds ratios (RORs) were calculated as the ratio of the odds of TKI-related CV events compared with CV events related to other anticancer drugs. Changes in RORs were noted to be event specific and they differed by TKI; some produced significant increases while others were associated with little to no response. Although a significantly increased ROR was noted for all TKIs except imatinib, dasatinib and bosutinib had the highest RORs for cardiac failure: 4.1, 95% CI, 3.7-4.6; and 3.5, 95% CI, 1.9-6.6, respectively.¹⁰

Nilotinib, ponatinib, and bosutinib significantly increased RORs relating to ischemic heart disease: 6.7, 95% CI, 6.2-7.2; 2.9, 95% CI, 2.4-3.5; and 2.5, 95% CI, 1.3-4.8, respectively. However, only nilotinib significantly increases ROR for cardiac arrhythmias (2.7, 95% CI, 2.1-3.5). Ponatinib was the only TKI associated with significant increases in adjusted ROR for hypertension (3.5, 95% CI, 2.9-4.3), with dasatinib demonstrating a significant increase for pulmonary hypertension specifically (8.5, 95% CI, 6.8-10.6).¹⁰

Regarding torsade de pointes/QT prolongation, nilotinib significantly increased adjusted reporting odds ratio (aROR); (12.2, 95% CI, 10.3-14.6) with noted significant aROR increases by dasatinib (2.5, 95% CI, 1.6-3.7).¹⁰ However, **Cortes** pointed out that a limitation of analyzing spontaneous reports is the introduction of reporting bias, in which clinicians may be more inclined to report events that they perceive to be drug related. “If you think that these things happened just because they happen on a 50-year-old [patient], you do not report them,” he said. “If you think it is the drug, you report them because this

is spontaneous; this is not a clinical trial where you are supposed to report it anyway.”

Available Options After Second-Generation TKI Failure

The phase 2 PACE trial (NCT01207440) was an open-label, multinational trial that evaluated ponatinib in patients with CML or Ph+ ALL who received previous therapies (37% had received 2 TKIs and 55% had received 3 or more TKIs prior to enrollment). By 12 months, in the subgroup of patients with CP-CML, 56% had an MCyR, 46% had a complete cytogenetic response (CCyR), and 34% had an MMR. Of the patients who had an MCyR, the median time to response was 2.8 months and the estimated rate of a sustained response for at least 12 months was 91%. **Cortes** also pointed out that in this study, patients who received fewer TKIs prior to enrollment tended to have a better response rate: In those who had received 1 approved TKI prior to enrollment, the MCyR rate was 79%, whereas it was 67%, 45%, and 58% in those patients who received 2, 3, and 4 TKIs, respectively.¹¹

“Getting that [response rate] after 3 previous TKIs is pretty good, but... do not hold your cards for later because later may be too late,” **Cortes** said.

Responses also appeared to be durable in the long term. Using Kaplan-Meier estimates, a follow-up analysis of 267 evaluable patients with CP-CML in the PACE trial showed that 82% of patients who achieved an MCyR by 12 months and 59% of patients who achieved an MMR at any point were expected to maintain these responses at 5 years. Of the patients with CP-CML in the safety population, at least 1 dose reduction was reported in 82% and at least 1 dose interruption of 3 or more days was reported in 82%; however, the data show that most patients maintained MMR despite these dose modifications. Post hoc analyses of 145 patients who were still using ponatinib showed that 96% of patients who had achieved an MCyR and then had a dose reduction continued to maintain their response after the reduction. Of the patients who had an MMR and a dose reduction, 90% maintained their response after dose reduction. In patients with no pre-emptive dose reduction, 94% and 95% of patients maintained their MCyR and MMR, respectively.¹²

“Certainly, it tells you that for a patient in whom it is appropriate to dose reduce because of toxicities, you can, and you should,” said **Cortes**.

Despite the efficacy of ponatinib, the AOE associated with its use require close monitoring in clinical practice.³ The 5-year follow-up data from the PACE trial showed that in the CP-CML subset, the rate of exposure-adjusted AOE was 14.1 patients with events per 100 patient-years.¹² **Cortes** added that the often-quoted rate of ponatinib-associated AOE

(approximately 30%) originates from criteria established by the FDA that include any symptom that could be remotely related to an AOE, such as indigestion-related chest pain and cold hands; the rate differs substantially from those listed on labels from the European Medicines Agency. To reconcile this rate discrepancy, an independent end point adjudication committee (EAC) including 3 cardiologists, a hematologist, and a neurologist performed a retrospective review to evaluate the rates of clinically relevant AOE associated with ponatinib in the PACE trial.¹³ Using American College of Cardiology/American Heart Association definitions of major adverse CV events, the investigators reviewed the type of event, severity, concomitant medication, and hospitalization data, then compared these results with Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA PT) search results. In the review, the EAC verified fewer AOE and serious AOE than were identified in the MedDRA PT search (17% vs 25% and 16% vs 20%, respectively), and the authors concluded that the risk for clinically relevant AOE based on data from the PACE trial may have been overestimated.¹³

Despite these findings, **Talpaz** cautioned that the rate of clinically relevant AOE warrants concern, and recommended minimizing the dose of ponatinib when possible. However, **Jabbour** and **Berman** said that the risk for AOE would not prevent them from using ponatinib, with **Jabbour** sharing that he would be mindful of a patient’s AOE risk factors but that the risk of AOE would not affect his use of ponatinib in practice.

MANAGEMENT OF CARDIOVASCULAR TOXICITIES: IN PRACTICE

The safety profiles relating to CV-related toxicities and events vary for each TKI and are often greater in those patients requiring chronic treatment.¹⁰ To minimize CV-related toxicities, **Mauro** suggested lowering the dose and shortening the duration of exposure to second-generation TKIs, but he noted that increasing CV monitoring could be difficult. “We don’t know exactly which tests are very informative,” he said, adding that he refers patients to a cardio-oncologist when they start taking ponatinib to get baseline tests and ensure that future CV events are not drug related. However, **Mauro** said that the CV risk is fairly small relative to the potential damage resulting from inadequate treatment of CML.

Smith shared that figuring out ways to safely lower the dose of a drug that is working for a patient when they are experiencing toxicities is critical. “You want to make sure you get a response if you move them to a third-generation drug like ponatinib, and then figure out the right timing of how to back off the drug to lower the longer-term risk,” he explained. »

Cortes added that the early enthusiasm about the high response rates seen with TKIs may have also lowered priority for management of comorbidities in the past. “We are starting to realize that we need to monitor these patients a little bit better and involve the cardio-oncologist, the nephrology [department, and] the endocrinologist in certain patients, when it’s needed,” he said.

Sweet said that she gives an angiotensin-converting enzyme inhibitor and aspirin (provided that platelet counts are adequate) to all patients starting on ponatinib, as well as those with a comorbidity who are starting on nilotinib. She also refers them to the cardio-oncology department. “I would rather have them be evaluated and have nothing come from that than miss something,” she said. Similarly, **Hobbs** said that she gets the patient’s primary care doctor, cardiologist, and pharmacist involved to help monitor patients on chronic oral drugs.

Talpaz said that he periodically monitors patients who are taking dasatinib with surface echocardiography; he reserves chest X-rays for those who report signs of pulmonary effusion. However, **Mauro** noted that some of the CV tests commonly used by oncologists, such as echocardiography, may not be the most useful for detection of arterial occlusion, whereas other less, recognized tests, such as the ankle-brachial index test, may be more helpful. “It is up to us, as a field, to figure out what other tests are really helpful to stratify the CML patient,” he said. **Cortes** added that AOE events generally occur from “a sum of risk factors” and that management of modifiable risk factors such as cholesterol level, diabetes, hypertension, and smoking could also be important for patients with CML who need a TKI.

Dose Reductions of Ponatinib

To evaluate whether dose reductions of ponatinib can reduce CV toxicity while maintaining efficacy, the OPTIC trial (NCT02467270) randomized patients with CP-CML who were resistant or intolerant to 2 or more TKIs or who had a *T315I* mutation to receive ponatinib at a starting dose of 45 mg (cohort A), 30 mg (cohort B), or 15 mg (cohort C) per day, with reduction of the dose to 15 mg upon reaching *BCR-ABL1* PCR of 1% or less in cohorts A and B.¹⁴ A trend toward a dose-response relationship was observed in the interim analysis, with a *BCR-ABL1* PCR of 1% or less achieved by 12 months in 38.7%, 27.4%, and 26.5% of patients in cohorts A, B, and C, respectively. Thirty-six of the 48 patients in cohort A and 24 of 33 patients in cohort B had dose reductions after achieving *BCR-ABL1* of 1% or less as per protocol (6 and 5 patients in cohorts A and B, respectively, had dose reductions before achieving *BCR-ABL1* of 1% or less).¹⁴ **Cortes** pointed out that all responses

that were lost or could not be maintained (9 patients in cohort A and 5 patients in cohort B) occurred within 90 days of dose reduction, sharing that these results “emphasize the need for close monitoring right after dose reduction.”

Patients who lost their response after dose reduction were allowed to receive dose reescalation, and 3 of 9 patients in cohort A and 2 of 4 patients in cohort B regained their response after reescalation.¹⁴ However, **Cortes** noted that the follow-up was short and that a couple of patients had regained their response since the interim analysis.

Cortes also pointed out that the higher rates of *BCR-ABL1* response with the highest dose appeared to be particularly pronounced in the subgroup with the *T315I* mutation, with rates of 42% in cohort A, 24% in cohort B, and 8% in cohort C, suggesting that the lower starting doses are not as effective in these patients.

An independent adjudication committee prospectively reviewed AOE events in the aforementioned OPTIC trial (which examined ponatinib use in patients with CP-CML who were resistant or intolerant to 2 or more TKIs or who had a *T315I* mutation) using definitions from the American College of Cardiology/American Heart Association, FDA, and Standardized Data Collection for Cardiovascular Trials Initiative and was blinded to dose, dose modification, and investigator opinion on the cause of the event.¹⁴ No AOE-related mortalities were reported, and the overall adjudication rate of AOE events was 3.5%, with rates of 5.3% (5 events) in cohort A, 4.3% (4 events) in cohort B, and 1.1% (1 event) in cohort C. **Cortes** commented that although these interim results may suggest a dose-dependent increase in AOE events, the dose-dependent increase in efficacy with the higher doses was more clinically meaningful, particularly for the subgroup with a *T315I* mutation.

Clinical interpretation of the OPTIC trial data was difficult for some of the panelists, but **Hobbs** said that having a study evaluating safety and efficacy of different dosing schedules is helpful for educating providers in the community setting about the safe use of ponatinib. “Ultimately, I think there [needs] to be a lot of education to get people comfortable with using this drug,” he pointed out.

Radich said that the interim data from the OPTIC trial may encourage more flexibility with dosing of ponatinib based on regular monitoring of response and tolerability.

NOVEL TKIS UNDER INVESTIGATION

TKI treatment options for patients with CML have increased considerably over the past decade, but inadequate treatment responses and intolerable AEs remain obstacles.¹⁵ Most TKIs target the ATP-binding pocket in

the kinase domain; however, mutations that commonly arise in this region can affect the efficacy of a treatment. Additionally, *T315I* mutations are common in patients with CML and lead to a high rate of resistance to most available TKI treatment options. Novel treatments that employ a different mechanism may help to alleviate some of the concerns and intolerances seen with the treatments currently used in practice. **Cortes** emphasized this point, stating, “It’ll be nice to have yet another *T315I*-[focusing] drug.”

HQP1351 (olverembatinib)

Olverembatinib is a novel, potent, oral, third-generation *BCR-ABL* inhibitor designed to effectively target a spectrum of *BCR-ABL* mutations.¹⁶ Two pivotal open, single-arm, multicenter phase 2 trials are under way to investigate its efficacy in patients with TKI-resistant and *T315I*-mutant CML (NCT03883100, NCT03883087).^{17,18}

Results from the first study (NCT03883087) demonstrated that within 41 evaluable patients without a CCyR at baseline, 75.6% attained an MCyR within the median follow-up of 7.9 months. Of those patients achieving an MCyR, 65.9% of patients obtained a CCyR and 9.8% attained a partial CyR (PCyR). Of the evaluable patients, 48.8% achieved an MMR within 12 months.¹⁶

Of the 23 evaluable patients without MCyR at baseline within study 2 (NCT03883100),¹⁷ 52.2% attained an MCyR, with an additional 39.1% and 13.1% achieving a CCyR and PCyR, respectively.¹⁶ An MMR was achieved in 26.1% of evaluable patients within the median follow-up of 8.2 months.¹⁶

Olverembatinib was well tolerated; the most common treatment-related AEs of all grades were thrombocytopenia (73.9%), anemia (65.2%), leukopenia (56.5%), and neutropenia (26.1%).¹⁶

PF-114

PF-114 is a fourth-generation oral TKI, an agonist for wild-type and mutated *BCR-ABL1* isoforms including *BCR-ABL1*^{T315I}. It is being investigated in a phase 1 study of patients with CP-CML or accelerated phase CML who have failed at least 2 TKIs or who have *BCR-ABL1*^{T315I} mutation and have undergone at least 6 months of therapy (NCT02885766).¹⁹ A total of 51 patients, many heavily pretreated, were enrolled: 25 had received at least 3 prior TKIs, and 5 patients with *BCR-ABL1*^{T315I} had received 1 prior TKI. A total of 6 patients achieved an MCyR, with an MMR noted in 67% (4/6). In patients with a *BCR-ABL1*^{T315I} mutation, 5 responded to treatment, and 4 of those (80%) attained an MCyR. **Cortes** noted that although only phase 1 data are currently available for olverembatinib and PF-114, the results are promising, with future studies under way for this agent.

Radotinib

Radotinib is an oral, high-affinity *BCR-ABL1* inhibitor.²⁰ The results of a phase 2 study (NCT01602952) in Ph+ ALL CP-CML patients with resistance and/or intolerance to *BCR-ABL1* TKIs showed that among 77 patients who took radotinib for a median of 378 days (range, 8-1050 days), 47% of patients reached a CCyR and 75% reached an MCyR by 12 months.^{21,22} MMR was attained in 22% of the patients who achieved MCyR. Although CCyR and MCyR rates were greater in those patients without a mutation in *BCR-ABL1*, in those patients with the mutation, 21% and 43% achieved a CCyR or MCyR, respectively. Thrombocytopenia and anemia—occurring in 24.7% and 5.2% of patients, respectively—were generally short-lived and managed successfully with dose reductions or interruptions.²²

Asciminib

Asciminib is a novel, potent, and specific *BCR-ABL1* TKI that acts as an allosteric inhibitor by engaging in an empty pocket at a site of the kinase domain where the myristoylated N-terminal of *ABL1* (an allosteric negative regulatory element lost on *BCR-ABL1* fusion) usually binds. The results of a phase 1 dose-escalation trial (NCT02081378) of patients with CML and resistance to or unacceptable AEs from 2 or more ATP-competitive TKIs showed that in the subgroup without a *T315I* mutation, 54% of patients without a CCyR at baseline had a CCyR in a median of 24 weeks, and 48% of evaluable patients had an MMR (*BCR-ABL1* PCR of 0.1% or less) by 12 months. Of the patients with a *T315I* mutation, 41% of those without a CCyR at baseline had a CCyR at a median of 8 weeks, 24% achieved an MMR, and 50% had improvement in molecular response by 12 months.¹⁵

The results of the phase 3 ASCEMBL trial (NCT03106779), which randomized patients with CP-CML previously treated with 2 or more TKIs to receive asciminib or bosutinib, showed that asciminib was associated with a higher rate of MMR at 24 weeks compared with bosutinib (25.5% vs 13.2%, respectively) and a lower proportion of patients who discontinued treatment due to AEs (5.8% vs 21.1%, respectively).^{23,24} During treatment, 2 deaths were reported in patients receiving asciminib (1 due to ischemic stroke, 1 due to arterial embolism), and 1 death (due to septic shock) was reported in patients receiving bosutinib.²⁴

Despite the efficacy results with asciminib,²⁴ **Cortes** noted that the deaths need to be evaluated further, and he and **Mauro** pointed out that assessment of drug-specific CV risks is difficult because of discrepancies in CV entry criteria across the trials. “We always need to take those things with some caution because they’re not talking about the same patients and the same events,” said **Cortes**. ■

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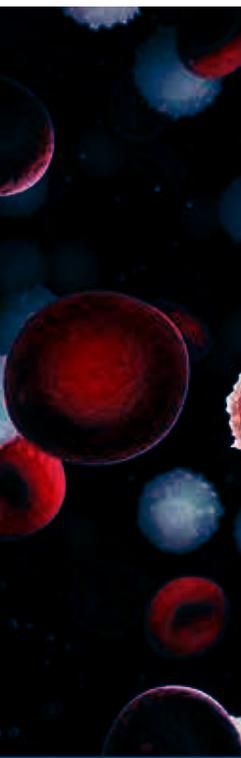
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INTRODUCTION

Editors from OncLive® spoke with Jorge E. Cortes, MD; Elias Jabbour, MD; Kendra Sweet, MD, MS; and Gabriela Hobbs, MD. These experts in hematologic malignancies provided insight on the current management of chronic myeloid leukemia, including the use of second-generation TKIs and the sequencing of therapies. Excerpts from their interviews* appear next.

**Interview transcripts are slightly edited for readability.*

Current and Future Trends in Chronic Myeloid Leukemia: Expert Perspectives



OncLive®: What are the currently approved treatment options for chronic myeloid leukemia (CML) and the factors you consider when choosing a treatment without head-to-head comparison data?

CORTES: Four drugs are approved for the frontline setting: imatinib and 3 second-generation tyrosine kinase inhibitors [TKIs]—dasatinib, nilotinib, and bosutinib. When you're facing a patient, the first consideration is whether you need a second-generation TKI or whether imatinib is appropriate. There are reasons why imatinib has some advantages in some instances. One advantage is cost, due to it being generic, but another is that it is associated with fewer arterial occlusive events [AOEs] and other adverse events, such as pleural effusions, than some of the other drugs.

The counterbalance to that is that you do get fewer of the patients getting to the deepest molecular responses, and the responses have been slower. For patients who are not aiming for treatment-free remission, and those in whom you have more concerns about AOEs, those are scenarios you may consider and say, "OK, maybe imatinib is the best

choice for these patients, at least to start with."

If you're going to use a second-generation TKI, which is what I choose for the large majority of my patients, then you need to decide which of the 3 to select. There's really no difference in efficacy among them. Actually, at ASH [the 62nd American Society of Hematology Annual Meeting and Exposition], the very first randomized study between 2 second-generation TKIs for de novo chronic phase [CP] CML was presented: the randomized phase 3 JALSG CML212 study from Japan. They randomized patients to dasatinib vs nilotinib and found no significant difference between the two, which is what we expected, but no randomized study had been done before this.

Considering that, other aspects to consider include the toxicities that you can expect; you base some of that on a patient's comorbidities. One drug may be more appropriate than another for a given patient. For example, if a patient has diabetes, nilotinib can make the management of diabetes [more difficult]. It's not a contraindication, but you may prefer to go to another drug. If the patient has pulmonary issues, I may not want to go with

dasatinib because of the risk of pleural effusions. If a patient has irritable bowel syndrome, already having a lot of bowel issues, I may not want to go with bosutinib because of the [associated] diarrhea. [In addition,] the schedule may be important. For some patients, the twice-a-day schedule with fasting of nilotinib may be complicated. Fortunately, you have other drugs that can be given once a day.

[Given] all of these factors, it's important to involve the patient—to understand their goals, how a given schedule fits with them—and to make a decision that works for them.

Onclive®: What is the prognosis for patients who develop resistance to second-generation TKIs? What options are available to them?

SWEET: The second-line setting depends on what you used in the frontline setting. If you started someone on imatinib, then, for the majority of patients, it makes sense to try a second-generation TKI in the second-line setting. This is unless a *T315I* mutation is present, in which case you go straight to ponatinib—no one would argue that point. However, if you've started somebody on a second-generation TKI up front, and the therapy fails not because of intolerance but because of resistance, most people in the CML world would probably agree that another second-generation TKI is unlikely to work in that setting. It's not impossible, but it's not likely to benefit the patient.

If it fails because of intolerance, however, that's a different story, and trying another second-generation TKI makes sense. Again, if you have failure on imatinib, then trying a second-generation drug makes sense. My opinion is that if someone is on a second-generation drug up front and they have resistance to that drug, ponatinib is the perfect drug to use in the second-line setting for that particular patient, [regardless] of whether or not a mutation is present. If they were on a second-generation TKI and they have a mutation that's resistant to that particular drug, perhaps another second-generation drug makes sense. In most cases, though, I think ponatinib makes sense if a patient has failed a second-generation drug.

Ponatinib was not seen as the optimal treatment option a few years back, in 2013, when it was temporarily pulled off the market because of AOE's from the PACE trial. Certainly, it warranted further investigation; no question. But looking back, we've realized that there's a lot we didn't know during that study. Had we known what we know now, I think the results of that study probably would have been a little bit different. I've used a tremendous amount of ponatinib over the course of the last 7 years, and I haven't seen toxicity anywhere near what was

reported back then, probably because we know [how to mitigate] the effects that were seen at that time.

Many people, including myself, are very cognizant of that and try very hard to mitigate those toxicities right up front with cardioprotective measures. We refer people to cardiologists up front to try to decrease risk of AOE's. I believe that makes a difference. I also think that some of the risk was a little bit overstated. A lot of hematologists were doing the work of cardiologists, and that doesn't always work out well. So a lot of things probably could have been done differently that would have changed that story.

But it is what it is, and certainly we have more updated data now that tell a slightly different story. It does not change the fact that ponatinib has risks—we know that, and we have to take those risks seriously. We have to consider those risks when we're choosing which patients to put on the drug. If you have a high-risk cardiovascular patient, perhaps ponatinib may not be the best option.

The truth is, though, for most patients we put on ponatinib, no better alternatives are out there. We're using the drug because it's the best therapy for their CML. We do as much as possible to mitigate risk from the drug and decrease its toxicity and hope for the best efficacy that we can get.

HOBBS: If a patient has a *T315I* mutation, for example, it's inappropriate to put them on any of the other second-generation drugs; instead, that person needs to be switched to ponatinib. Also, other mutations could determine whether the person is resistant to dasatinib, nilotinib, or bosutinib, and so those should be used to make a decision.

It is appropriate to switch patients between second-generation drugs. If they didn't have a great response to dasatinib, switch them over to nilotinib, but keep in mind that the potency among those drugs is comparable. Those drugs are much more potent than imatinib, but among themselves, the potency is not as significant. If a patient didn't have a good response to a drug like dasatinib or nilotinib up front, it's possible they won't have a response to a second-generation drug. Data are conflicting in that regard. I would have a low threshold to consider ponatinib for those patients, as well. Those are patients you have to be more watchful of. If they have frank resistance, or primary resistance, you have to keep a close eye on them.

CORTES: It's more challenging when the patient's first drug was a second-generation TKI because we don't have much information on what's ideal for these patients [for their next step]. Because these drugs are fairly equivalent, going to another second-generation TKI may not offer a big advantage. Ponatinib is available, and although there are no data, »

prospectively, in that context, it seems to be what we consider probably the best option for [such] a patient. However, this is with the understanding that we don't have prospective data to demonstrate that that's really the case.

JABBOUR: I choose ponatinib for those patients with an acquired *T315I* mutation and for those who failed a second-generation TKI. In my practice, I will not wait for multiple failed lines of therapy. For therapy that has failed once and the patient has second-generation TKI resistance, I will move to ponatinib, because if they take second-gen TKI, the complete cytogenetic response rate is only 24%. If you move to ponatinib, you can have a way higher response rate: 50% to 60%.

For ponatinib, we have to consider what dose to give. The approval was 45 mg per day, and based on the PACE trial, it's recommended to reduce the dose to 30 mg [or] 15 mg, once an optimal response is achieved.

OncoLive®: Do you anticipate ponatinib moving into an earlier-line setting?

CORTES: Some recent information on ponatinib will, I think, help us better manage the drug and potentially use it earlier. This recent study, the OPTIC trial, randomized patients to receive 1 of 3 starting doses: standard dose—45 mg—or 30 mg or 15 mg. An

important component of that study is that once patients achieved a response, which was defined as *BCR-ABL1* transcript levels of 1% or less, they were mandated to reduce the dose to 15 mg daily. The [results] suggest that 45 mg still offers the best benefit, particularly for the more difficult-to-treat patient population: the ones with the *T315I* mutation, those who have received more prior TKIs, and those who have not had even a cytogenetic response to the prior TKI.

Another thing we saw was that the risk of AOE appears to be much less than we had seen before, although this is an early look at the data. Some of [the lessened risk] may have been due to a better selection of patients, but it was likely also due to the dose reduction and better management of the comorbidities.

So I think that we are starting to learn how better to use ponatinib, and that will definitely help us use it in the patients in whom it's indicated. There's no reason why you should avoid it in a patient who has a *T315I* mutation or has gone through 2 TKIs or more. Then [another] question is whether we could move it to an earlier-line setting. For example, in the context of failure of 1 prior TKI, when that was a second-generation TKI used as frontline, ponatinib would probably give us the best chance of response, in my opinion. We've been hesitant because of these AOE. With this new information, perhaps I would be a lot more willing to do that for a given patient.



“We are starting to learn how better to use ponatinib, and that will definitely help us use it in the patients in whom it's indicated.”

—Jorge Cortes, MD

OncoLive®: Can you describe the findings from the OPTIC trial and how they impacted the utility of ponatinib?

SWEET: Again, the OPTIC trial looked at various doses of ponatinib, starting at higher doses and lowering the dose when people met response. It determined whether patients could maintain response once the dose was lowered, and it looked at toxicity, dependent on what dose they were started at.

There’s a lot to interpret within these data, and it takes some focus to really understand what they’re saying. But overall, I think [the results indicate] that people need to be started at 45 mg. The toxicity improves when we lower the dose of the drug. We thought that before, and we know that now. We know that patients with a *T315I* mutation respond better than patients who don’t have a *T315I* mutation, partially, I think, because those patients have fewer prior lines of therapy.

[That leads to] another key point of the study: that potentially using ponatinib earlier on, in earlier lines of therapy, may benefit patients. If you use it as fourth-line therapy, they may not respond as well as if you use it in the second-line setting. Some of the [decision] is dictated by insurance more than anything else, for better or for worse, [but] we do know that fewer prior lines of therapy lead to better responses with ponatinib. We know that starting at 45 mg leads to better response in the majority of patients, but that toxicity improves as you lower the dose.

I think we learned a lot from that study, and the toxicity data were encouraging. Again, the toxicity is there—we don’t want to make light of that because it’s still there; it’s real. But it’s a lot less than it was on PACE, and that’s meaningful. These data are clinically useful, clinically meaningful. I think a lot of us were doing something similar in clinical practice already, as far as starting patients at a higher dose and trying to dose-reduce as soon as we felt like it was the right time, as soon as they were getting some clinical response. It’s good to see [results] that support that type of clinical practice, rather than just people doing it because it seems to make sense.

HOBBS: These ongoing studies that were presented at ASH, included the PACE and OPTIC studies, are trying to look at long-term safety as well as safety and efficacy of starting patients at the 45 mg dose and then decreasing those patients to 30 mg or to 15 mg. [The goal is] to see if once a patient has achieved a remission, you can maintain that remission on a lower dose and also lower the likelihood of cardiovascular toxicity. It will be important [to see] these studies published, and not just in abstract form as they were presented at ASH [2020].

I would say that as data have accumulated, all of us who use ponatinib know that it is a fantastic drug that has a real role in the care of our patients with CML. If used properly, I believe that it is a safe medication. Obviously, it has toxicities, as all the TKIs do. If you’re starting a patient on ponatinib, to optimally manage them, it’s important to have them on an aspirin, to check their lipid panel, and to have a relationship with a cardiologist or primary care doctor, or a cardio-oncologist if you’re fortunate to have that at your center. I think that’s probably true of nilotinib, as well.

OncoLive®: Looking to the future, what investigational TKIs or other agents look particularly promising in the frontline, second-line, or later-line settings?

CORTES: Perhaps the most interesting and most groundbreaking study was ASCSEMBL, a randomized study of asciminib vs bosutinib. Asciminib, as we know, is a novel TKI. It’s called a STAMP inhibitor, because it binds into the ABL myristoyl pocket. It has a completely different mechanism of action. We’ve seen the initial results from the phase 1/phase 2 study, but this is the first randomized study in later lines of therapy, with patients who had received 2 or more TKIs. It did not include patients with *T315I* mutations because the control arm was bosutinib, where we know it doesn’t work.

Excluding those patients, the efficacy was significantly better. The primary end point was major molecular response [MMR] at 24 weeks, and it was 25.5%, compared with [about] 13.2% for bosutinib [(95% CI, 2.19-22.3); 2-sided *P*= .029]. That’s an early response, but many other benefits emerged, including complete cytogenetic response. It seems to be very well tolerated. Again, we need to be cautious—[this is an] early look—and we need to see further [results]. Still, the experience we’ve had with asciminib has been very favorable, so I think this is a very important study, a pivotal study. Of course it has to be reviewed by the regulatory authorities, but we hope that [the FDA] will make asciminib available in the clinic very soon.

Another study that was presented looked specifically at asciminib in patients with *T315I* mutation; it does work in these patients. A higher dose is necessary, but [the results] showed the efficacy of the drug [in that scenario]. An interesting part of that presentation is that the patients were divided: those who had and who hadn’t previously received ponatinib. You do lose a little bit of the response when patients had already received ponatinib, but it’s still a very good response rate of about 25% to 30% MMR. [The results] show that it’s a very potent drug, even in the most complex settings. »

We need to keep an eye on a couple of new drugs that are early in their development. An analysis of one of them, HQP1351, presents data on patients with *T315I* mutations, and it has a very good activity with what appears to be a good safety profile, as well. The other drug is vodobatinib, or K0706. It doesn't work against *T315I* mutations, but in all the other mutations it showed a very good response rate, both in patients with and without prior exposure to ponatinib.

Again, these 2 drugs are just emerging, but I think that in the future, number 1, we're going to have more treatment options. I expect asciminib to be approved, and I hope that one or both of the other ones that I mentioned could be approved eventually. Second, more and more, we're looking at how we can better manage our patients. We're paying more attention to comorbidities and managing the patient in a more integral way and not just [focusing on] the polymerase chain reaction [PCR]. Of course, we continue to try to improve the probability of getting patients to a treatment-free remission.

OncoLive®: Can you provide some closing thoughts on the future treatment landscape for CML?

HOBBS: Treatment for CML has come a long way in the past couple of decades. As I mentioned earlier, I think we are very fortunate to have drugs in the first-line, second-line, and third-line settings in CML. All 5 TKIs that are approved right now are really wonderful. I think for the vast majority of patients with CML, we can—as their physicians or practitioners—offer a lot of hope and expect that most patients with CML are going to have a normal, or near normal, life expectancy.

However, as people that take care of patients with CML, [we must] remember that patients who don't take their medication definitely have the potential of developing really difficult-to-treat disease. Also, we shouldn't be complacent, as providers, just because these patients with CML look fine and they're not patients who are receiving chemotherapy. Although some of them may have some chronic toxicities, when we see them, outwardly, they look OK, and even if they're not in a great remission, their complete blood counts are probably normal.

[For those reasons, it can be] hard to remember that bad CML is still really difficult-to-treat leukemia. You [can] go from a leukemia that you can treat with a TKI forever to a leukemia that can only be treated with a transplant. Our goal as providers should be to try to avoid that at all costs. I encourage everybody to follow the National Comprehensive Cancer Network guidelines. Make sure that these patients with CML are monitored according to those guidelines, with

PCR testing done at regular intervals, initially at least every 3 months, to make sure that they do meet [the appropriate] landmarks and that they are offered the possibility of a normal life expectancy.

In terms of treatment, I always feel very optimistic with CML. Patients have the possibility of really great outcomes. Those patients who don't respond to initial therapy or to second-line therapy have lots of options now, I think. We have 3 second-generation drugs with excellent potency. We're also learning much more about ponatinib, how to give it safely, and I think that's really important.

Treatment-free remission is probably one of the most exciting things that's happened with CML since we've had TKIs to treat it. I think it's important to keep in mind which patients are candidates for treatment free remission or for discontinuation of their TKI.

Some patients do very well with discontinuation. I'm excited to see research in this area to help us better identify who will be successful off their TKI. It's definitely something worth considering for those patients who are candidates, but it's also important to monitor these patients appropriately when you do discontinue their TKI.

CORTES: I'd also [like to] mention, from ASH, the report from the International Chronic Myeloid Leukemia Foundation on patients with CML who have COVID-19 [coronavirus disease 2019]. It's very topical, and also it was a great international effort, collecting [valuable data about] all the patients who had been seen by different investigators and physicians from all over the world. All continents were represented. The report showed that most patients, fortunately, had mild or moderate disease. A subset of patients, about 20%, had severe disease, meaning they ended up in the intensive care unit or intubated or [some other dire situation], and the mortality rate was about 10%. It wasn't quite as high as for other cancers, but it was higher than the general population. The results didn't show that any particular TKI affected [outcome]. [In most cases,] the mortality came from the patients who had risk factors that were recognized—older age, all the comorbidities, and so forth.

This is all important information, because unfortunately, COVID-19 is something we're living with today. The information is useful [to have] to be able to guide our patients and for other physicians who are caring for these patients. ■

To hear more about current and future trends in chronic myeloid leukemia from these experts and others, visit <https://bit.ly/39BZx24>.

