Transcript Details
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Addressing TKI Resistance in Patients with CML

Dr. Caudle:
Tyrosine kinase inhibitors, or TKIs, have dramatically changed the therapeutic landscape and improved outcomes for patients with CML, with relative survival being similar to the general population.[1]But for those who've experienced TKI failure, sequential use of 2nd-generation TKIs in the third-line setting is associated with suboptimal outcomes in chronic phase CML.[2-4]

On today's program, we'll take a closer look at CML through the lens of a 3rd-generation pan-mutational treatment option specifically designed to overcome TKI resistance, including in patients with T315I positive CML.

This is ReachMD, and I'm your houst Dr. Jennifer Caudle.

And joining me today is Dr. Javier Pinilla-Ibarz, Senior Member and Head of the Lymphoma Section in the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida. Dr. Pinilla is a paid consultant for Takeda.

Dr. Pinilla, welcome to the program.

Dr. Pinilla:
Thank you very much. I'm very happy to be here today.

Dr. Caudle:
So, to start, Dr. Pinilla, let's get a better understanding of TKI therapy failure. What are some of the challenges for patients who have experienced TKI failure?

Dr. Pinilla:
First of all, let's define TKI failure. We can really encounter, uh, primary resistance when patients do not really achieve a classical NCCN milestones but they are really very well documented at 3 or 12 months versus the secondary resistance.[5] Secondary resistance in-imply when patient has a very good response most of the time complete cytogenetic response and they lose this response.[6]

Obviously, patients can develop primary and secondary resistance to first or second generation BCR-ABL TKI regardless of T315I mutation status.[7] Among patients with BCR-ABL mutations the frequency of the T315I mutation was between 10 to 27% of cases.[8]

This is why measuring BCR-ABL levels is very important to really monitor the patients with CML on therapy as well testing for mutation is also very relevant when we really try to understand why patients are failing first or second generation TKIs.

Dr. Caudle:
Dr. Pinilla, let's turn to the treatment option of ICLUSIG®, also known as ponatinib, which I understand is the only 3rd-generation TKI in CML. But before we continue, let's review the full indication, Limitations of Use, and Boxed Warning.

Announcer:
ICLUSIG® is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-postive CML (chronic phase, accelerated phse, or blast phase) or T315I- positive Ph+ALL.

Limitations of Use:
ICLUSIG® is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Important Safety Information:
Warning arterial occlusive events, venous thromboembolic events, heart failure, and hepatotoxicity.

See full prescribing information for complete Boxed Warning.

- Arterial occlusive events (AOEs), including fatalities, have occurred in ICLUSIG®-treated patients. AOEs including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events.Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG® based on severity. Consider benefit-risk to guide a decision to restart ICLUSIG®.
- Venous Thromboembolic events (VTFs) have occured in ICLUSIG®-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG® based on severity.
- Heart failure, including fatalities, occurred in ICLUSIG®-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ICLUSIG® for new or worsening heart failure.
- Hepatoxicity, liver failure and death have occurred in ICLUSIG®-treated patients. Monitor liver function tests. Interrupt or discontinue ICLUSIG® based on severity.

Additional important information will be provided later in this program.

Dr. Caudle:
So, Dr. Pinilla, what do we need to know about ICLUSIG® to start?

Dr. Pinilla:
So, ICLUSIG®, also known as ponatinib, is the only third generation pan-mutational TKI that has shown activity against all single point mutations that causes resistance to the first or second generation TKIs.[5,9-11] Specifically, this medication, uh, was designed to overcome these BCR-ABL mutation, including the most difficult-to-treat mutations such T315I.[10,12]

Dr. Caudle:
Shifting gears, Dr. Pinilla, can you walk us through your rationale for incorporating ICLUSIG® into your treatment plans as opposed to using another 2nd- generation TKI in the third line?

Dr. Pinilla:
That's a great question. Complete cytogenetic responses rate when cycling through second generation TKIs are low. They are being reported less than 20% in the third line particularly with patients are resistant to a prior therapy.[2-4]That's the reason there is critical action window for CML patients after treatment failure with two prior TKI. In my opinion, there's a very good opportunity to be move beyond cycling through other second generation TKIs.

Dr. Caudle:
Now staying on that track, Dr. Pinilla, how do you determine which patients are the appropriate candidates for ICLUSIG®?

Dr. Pinilla:
Well, there is two common scenerios where we really thinking about the use of ICLUSIG® .

Number one, when patient are resistant to previous BCR-ABL but we don't find any specific mutation in the ABL gene. This is happen classically with patients on therapy through, uh, two second-generation TKIs, has increased level of BCR-ABL and many times they lose cytogenetic response or they may never achieve that previously.[5]

In contrast, when we really find mutations is another situation where really this drug is extremely useful. When we find mutation we already mentioned before that the most classical mutation is the T315I mutation and in this situation, w- this is specific mutation, the use of, um, ICLUSIG® can be, and regardless of the line of therapy as we can really find this mutation after only one line of therapy.[5] Overall and in general, this drug also is able to cover any other single mutation and is able to overcome that.

Dr. Caudle:

And what can you tell us about the study design and patient eligibility of the two key trials for ponatinib?

Dr. Pinilla:
ICLUSIG® or ponatinib was evaluated in two key studies.

The PACE trail and the OPTIC dose-optimization trial.[5,13,14] Both trials enrolled patients with chronic phase CML who had experienced resistant to two prior TKIs, although patients who had failed three TKIs also was part of these trials.[5] Also, r- um, these patients who has T315 mutation were able to be enrolled. In the OPTIC trial, patients with uncontrolled hypertension, diabetes, or clinical significant uncontrolled or active cardiovascular disease were excluded.[5]

Dr. Caudle:
And what do the long-term efficacy data from PACE tell us about ICLUSIG® for treatment- resistant patients?

Dr. Pinilla:
The PACE study had a 45 mg starting dose with a continuous treatment.[5] And in this sense, it delivered a long-term, 5-year response and survival in patients with chronic phase CML regardless of mutation status in a very tough-to-treat patient population. The summary of the 5-years chronic phase data from the PACE are as such: overall major cytogenetic response by 12 months in 55% of the patients, that is the primary endpoint of the trial[5] with a 73% overall survival[13] and 53% progression-free survival.[13] The 5-years estimated overall survival and progression-free survival were consistent also in patients with T315I.[5]

Serious adverse reaction occurred in 69% of the patient[5] and adverse events or serious adverse events in more than 2% of the patients included arterial occlusive events, pneumonia, cardiac arrythmias, pancreatitis, lipase elevation, abdominal pain, cardiac failure, hemorrhage, sepsis, VTEs, fluid retention, edema, pyrexia, secondary malignancies, anemia, hypertension, thrombocytopenia, febrile neutropenia, cellulitis, and arthralgia.[5]

Fatal adverse event occur in 9% of the patient and the most frequent were arterial occlusive events, sepsis, and hemorrhage.[5] The cumulative arterial occlusive event was around 25%.[13]

And what I have seen in these, uh, in my practice with the use of this drug, the efficacy data it reflect the good, um, use of this drug in, uh, heavily pre-treated population of chronic phase CML. And regarding, um, the side effects in my practice, I have seen mostly the, uh, high blood pressure, uh, pancreatitis, lipase elevation and abdominal pain. Uh, However, in terms of arterial occlusive events through, uh, very close collaboration with a cardio-oncology and try to minimize, if not reduce, the, uh, possible cardiovascular risk factors.

Dr. Caudle:
Dr. Pinilla, let's explore the evidence supporting ICLUSIG® as a third-line treatment option for CML with a closer look at the OPTIC trial, which is a unique study because it includes a proactive response-based dosing regimen.[5,14] What were some key takeaways from this study?

Dr. Pinilla:
As you pointed out, ICLUSIG® in this trial was investigated looking for the optimal usage in a proactive response-based strategy.

The starting doses of 45 mg were reduced to 15 mg once patient achieved less than 1% of BCR-ABL.[5] Once again, was a challenging patient population of difficult-to-treat TKI resistant patients where 99% of patient had failed at least two prior TKIs[5] and 98% were resistant to prior TKI.[5]

In terms of results, 44% of patients achieve the primary endpoint of less than 1% of BCR-ABL at 12 months, regardless of the T315I mutation status.[5] In this case, the maximum benefit to risk ratio, uh, was seen starting at the dose of 45 mg while maintaining the long-term efficacy at the reduced dose of 15 mg.[5]

Serious adverse reaction occur in 34% of patients with chronic phase CML who received ICLUSIG® at starting dose of 45 mg in the OPTIC trial.[5] Serious adverse reaction in more than 2% of patients included arterial occlusive events, cardiac arrythmias, thrombocytopenia, pyrexia, anemia, abdominal pain, atrial fibrillation, pancreatitis, and lipase elevation, neutropenia, and hypertension.[5] Fatal adverse reaction occur in 2.1% of the patients, both of which were sudden deaths.[5]

Dose modification due to adverse reaction occurred in 71% of patient who received ICLUSIG® at 45 mg for starting dose and 19% of patients required permanent discontinuation following an adverse reaction.[5] In my opinion, uh, from the OPTIC analysis, ICLUSIG® achieved and maintained a very clinical meaningful depth of response of TKI-resistant CML patients with an excellent risk/benefit ratio in

terms side effects seen in this trial.[5]

Dr. Caudle:
My last question for you, Dr. Pinilla: is that given everything we covered today, are there any takeaways you want to impart for our CML-treating audience?

Dr. Pinilla:
So, in my practice and my experience, every time that I've really considered the use of ICLUSIG®, I really, uh, do a risk/benefit, uh, decision and I consider the patient individual, uh, characteristics and comorbidities m- mainly, uh, cardiovascular, uh, risk factors. Uh, however, in my personal ex- experience and in my practice, I have a very, very good response with this medication, but this not be reflected of, uh, what has happened with other providers or other patients with the use of this drug.

Dr. Caudle:
Thank you, those are great practical takeaways for us to come away with. And I'd like to thank my guest, Dr. Pinilla, for helping us better understand the role of ICLUSIG® in third-line treatment for patients with chronic-phase CML.

Dr. Pinilla, it was great speaking with you today!

Dr. Pinilla:
Thank you very much. It was my pleasure.

Dr. Caudle:
And before we close, let's take a moment to review some important safety information.

Announcer:

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG® in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. The incidence of AOEs in OPTIC (45 mg->15 mg) was 14% of 94 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In OPTIC and PACE, AOEs were more frequent with increasing age.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded. In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG® were excluded. Consider whether the benefits of ICLUSIG® are expected to exceed the risks.

Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG® based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG®.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG®. In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. VTEs included deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG® based on recurrence/severity.

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG®. In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue ICLUSIG® for new or worsening heart failure.

Hepatotoxicity: ICLUSIG® can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG® in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL. Hepatotoxicity occurred in 28% of 94 patients in OPTIC and 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in OPTIC (6% of 94 patients) and PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at a reduced dose or discontinue ICLUSIG® based on recurrence/severity.

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred in patients who received ICLUSIG®. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop ICLUSIG® if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG® and consider evaluating for renal artery stenosis.

Pancreatitis: Serious or severe pancreatitis has occurred in patients who received ICLUSIG®. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2 weeks. Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG® based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

Increased Toxicity in Newly Diagnosed Chronic Phase CML: In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with CP-CML, single agent ICLUSIG® 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG ® arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG®-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. ICLUSIG® is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy: Peripheral and cranial neuropathy occurred in patients in OPTIC and PACE. Some of these events in PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG® based on recurrence/severity.

Ocular Toxicity: Serious or severe ocular toxicity leading to blindness or blurred vision have occurred in ICLUSIG®-treated patients. The most frequent ocular toxicities occurring in OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG®. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG® based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG®. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG® based on recurrence/severity.

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, occurred in patients in OPTIC and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led to hospitalization. Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG® based on recurrence/severity.

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in OPTIC and PACE. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1 x 109/L or

platelets less than 50 x 109/L, interrupt ICLUSIG® until ANC at least 1.5 x 109/L and platelets at least 75 x 109/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG®-treated patients in OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG®.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG®. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG® until resolution. The safety of resumption of ICLUSIG® in patients upon resolution of RPLS is unknown.

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG®. Withhold ICLUSIG® for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG® after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG®. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG® can cause fetal harm when administered to a pregnant woman Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG® and for 3 weeks after the last dose.

ADVERSE REACTIONS
The most common (>20%) adverse reactions are rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-817-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Strong CYP3A Inhibitors: Avoid coadministration or reduce ICLUSIG® dose if coadministration cannot be avoided.
Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS
Lactation: Advise women not to breastfeed during treatment with ICLUSIG® and for 6 days following last dose

Females and Males of Reproductive Potential: Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG®. Ponatinib may impair fertility in females, and it is not known if these effects are reversible.

Pre-existing Hepatic Impairment: Reduce the starting dose of ICLUSIG® to 30mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function.

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