Written By: Jessie Signorelli, PharmD, BCOP
Massachusetts General Hospital

Positive Quality Intervention: Ponatinib (Iclusig®) Patient Management

Description: This PQI will aim to review ponatinib efficacy and safety data as well as clinical pearls regarding supportive care and adverse event management.[1]

Background: Ponatinib (Iclusig®) is a third-generation tyrosine kinase inhibitor (TKI) with activity directed at BCR-ABL mutant kinase in patients with chronic phase (CP) chronic myeloid leukemia (CML) with intolerance to at least two prior TKIs or with a T315I mutation. Ponatinib is also approved for accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other TKIs are indicated or who have a T315I mutation.

Safety and efficacy data of ponatinib in patients with CML or Ph+ ALL was first demonstrated in a single-arm, open-label, international, and multicenter trial, the PACE trial, which included patients with unacceptable side effects from dasatinib or nilotinib or a T315I mutation. A major molecular response (MMR) was achieved in 40% of patients with CP-CML (35% relapsed/intolerant to previous TKI, 58% in patients with T315I mutation). A major hematologic response (MaHR) was demonstrated in 61%, 31%, and 41% in the AP-CML, BP-CML, and Ph+ ALL, respectively. Median time to MaHR was 0.8 months (range 0.4-6.3), 1 month (range 0.4-4 months), and 0.7 months (range 0.4-6 months) in the AP-CML, BP-CML, and Ph+ ALL groups, respectively.[2]

The OPTIC trial was a dose optimization trial to explore the relationship between ponatinib dose and both adverse events and response. This trial demonstrated ponatinib can be safely decreased to 15 mg in CP-CML once BCR-ABL1 $\leq$ 1%.[3]

Ponatinib carries black box warnings for arterial occlusive events (AOEs), venous thromboembolic events (VTEs), heart failure (HF), and hepatoxicity. Other warnings associated with ponatinib include hypertension, pancreatitis, ocular toxicity, myelosuppression, and impaired wound healing.[1] Grade 3 or 4 adverse events (AEs) were seen in 89% and 67% of patients in the PACE and OPTIC populations, respectively.[2,3] Because there is a lag time between dose change and event risk, patients with CP-CML should be decreased to 15 mg once BCR-ABL1 is $\leq$1%.[4] Due to the number of AEs with ponatinib, monitoring and patient education are vital to decrease risk of serious AEs.

PQI Process: Upon receipt of new prescription for ponatinib:

- Verify patient has BCR-ABL1 mutation and one of the following indications:
  - CP-CML with resistance or intolerance to at least two prior TKIs
  - AP/BP-CML or Ph+ ALL whom no other TKIs are indicated (ex: developed AP/BP while on alternate TKI)
  - CML or Ph+ ALL with T315I mutation
  - TKI resistance in CP-CML per NCCN: Patients with >10% BCR-ABL1 IS at 6 and 12 months
- Verify dosing:
  - CP-CML: 45mg once daily with a decrease to 15 mg once daily once BCR-ABL1 $\leq$1%
  - AP-CML, BP-CML, and Ph+ ALL: 45 mg once daily
  - Hepatic impairment (Child-Pugh A, B, or C): decrease starting dose from 45 mg to 30 mg
  - Consider decreased starting dose of 30 mg in patients who may not tolerate a starting dose of 45 mg (ex: severe coronary artery disease, history of severe pancreatitis, or advanced HF)
- Dispensing information:

Written By: Jessie Signorelli, PharmD, BCOP
Massachusetts General Hospital

  - Ponatinib is a limited distribution medication; will first go to AcariaHealth pharmacy
  - If ponatinib is needed urgently, prescription should read "blast crisis" or "emergency"
  - For more information on dispensing, visit: Iclusigdirect.com or call 1-833-291-2773. Hours of operation are 8:30am to 8:00pm EST
  - Ponatinib is available as 10 mg, 15 mg, 30 mg, and 45 mg tablets
- Screen for drug interactions:
  - Advise patients to avoid grapefruit products as it may increase the amount of ponatinib in their blood and therefore increase their risk of adverse reactions
  - Avoid coadministration with CYP3A4 strong inducers
  - Increase QTc monitoring with concomitant QTc prolonging medications
  - If coadministration with CYP3A4 inhibitors cannot be avoided, decrease dose as follows:

Recommended ponatinib dose for coadministration with strong CYP3A4 inhibitors	
Current ponatinib dose	Recommended ponatinib dose with strong CYP3A4 inhibition
45 mg once daily	30 mg once daily
30 mg once daily	15 mg once daily
15 mg once daily	10 mg once daily
10 mg once daily	Avoid coadministration

- Laboratory monitoring:
  - Baseline: CBC, CMP, ECG, Mg, fasting glucose, lipid panel, blood pressure, comprehensive eye exam, TLS labs, consider baseline ECHO/MUGA, clinical cardiovascular assessment
  - Every 2 weeks for the first 3 months, then monthly or as clinically indicated: CBC
  - Every 2 weeks for the first 2 months then monthly or as clinically indicated: lipase
  - Monthly or as clinically indicated: LFTs, ECG
  - If concern for pancreatitis: amylase, lipase, triglycerides
- Dosage modification for adverse reactions: See supplemental

Dose reduction	**Dosage for Patients with CP-CML**	**Dosage for patients with AP-CML, BP-CML, and Ph+ ALL**
First	30 mg once daily	30 mg once daily
Second	15 mg once daily	15 mg once daily
Third	10 mg once daily	Permanently discontinue in patients unable to tolerate 15mg once daily
Subsequent reduction	Permanently discontinue in patients unable to tolerate 10mg once daily	

- Supportive care:
  - Patients with cardiovascular risk factors should be referred to a cardiologist[5]
  - Blood pressure should be well controlled prior to starting ponatinib if possible
  - Consider optimizing cardiovascular disease (CAD) risk factors including diabetes, hypertension, hyperlipidemia, history of CAD including myocardial infarction
  - Consider statin therapy if indicated: to decrease risk of drug interactions, consider a statin that is not a substrate of CYP3A4 including rosuvastatin or pravastatin, especially if for the

Written By: Jessie Signorelli, PharmD, BCOP
Massachusetts General Hospital

treatment of Ph+ ALL where patients will be on multiple chemotherapy and supportive care medications
    - Consider aspirin 81 mg PO daily for CAD event prophylaxis, however, there has not yet been data demonstrating the benefit of this intervention[6]

Patient Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet
- Administer with or without food
- If a dose is missed, skip the dose and take the next dose at the regularly scheduled time
- Educate patients how to monitor their blood pressure, log recordings and bring to appointments
- Monitor patients for signs or symptoms of bleeding and advise patient to contact provider with any of the following: vomiting blood or vomit that looks like coffee grounds, pink/brown urine or red/black/tary stools, coughing up blood/clots, unusual bleeding/bruising of skin, menstrual bleeding that is heavier than normal, unusual vaginal bleeding, nose bleeds that happen often, drowsiness/difficulty being awakened, confusion, headache, or change in speech [2]
- Educate patients to contact provider if surgery is planned, as ponatinib can impair wound healing
    - Withhold ponatinib treatment for ≥ 1 week prior to elective surgery and do not administer for ≥ 2 weeks following major surgery and until adequate wound healing [1]
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. ICLUSIG (ponatinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America, Inc.
2. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018 Jul 26;132(4):393-404.
3. Cortes JE, Apperley J, Lomaia E, et al. OPTIC primary analysis: a dose-optimization study of 3 starting doses of ponatinib. J Clin Oncol. 2021;39(15).
4. Dorer DJ, Knickerbocker RK, Baccarani M, et al. Impact of dose intensity of ponatinib on selected adverse events: Multivariate analyses from a pooled population of clinical trial patients. Leuk Res. 2016 Sep;48:84-91. doi: 10.1016/j.leukres.2016.07.007. Epub 2016 Jul 22. PMID: 27505637.
5. NCCN Clinical Practice Guidelines in Oncology. Chronic myeloid leukemia. Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
6. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016 Aug;30(8):1648-71. doi: 10.1038/leu.2016.104. Epub 2016 Apr 28. PMID: 27121688; PMCID: PMC4991363.

Recommended dose modifications for ponatinib for adverse reactions		
Adverse reaction	**Severity**	**Ponatinib dose modifications**
Arterial occlusive event (AOE) Cardiovascular or cerebrovascular	Grade 1	Interrupt ponatinib until resolved, then resume at same dose
	Grade 2	Interrupt ponatinib until Grade 0 or 1, then resume at next lower dose Discontinue ponatinib if recurrence
	Grade 3 or 4	Discontinue ponatinib
AOE: peripheral or vascular and other OR venous thromboembolism	Grade 1	Interrupt ponatinib until resolved, then resume at same dose
	Grade 2	Interrupt ponatinib until Grade 0 or 1, then resume at same dose If recurrence interrupt until resolution, then resume at next lower dose
	Grade 3	Interrupt ponatinib until Grade 0 or 1, then resume at next lower dose Discontinue ponatinib if recurrence
	Grade 4	Discontinue ponatinib
Heart Failure	Grade 2 or 3	Interrupt ponatinib until Grade 0 or 1, then resume at next lower dose Discontinue ponatinib if recurrence
	Grade 4	Discontinue ponatinib
Hepatotoxicity	AST or ALT > 3x ULN	Interrupt ponatinib until Grade 0 or 1, then resume at next lower dose
	AST/ALT $\geq$ 3x ULN, bilirubin > 2x ULN, ALP < 2x ULN	Discontinue ponatinib
Pancreatitis and elevated lipase	Serum lipase > 1-1.5 x ULN	Consider interrupting until resolution, then resume at same dose
	Serum lipase > 1.5-2 x ULN, 2-5 x ULN and asymptomatic, or radiologic pancreatitis	Interrupt until Grade 0 or 1 (< 1.5 x ULN) then resume at next lower dose
	Serum lipase > 2-5 x ULN and symptomatic, symptomatic Grade 3 pancreatitis, or serum lipase > 5 x ULN and asymptomatic	Interrupt ponatinib until complete resolution of symptoms and after recovery of lipase elevation Grade 0 or 1, then resume at next lower dose
	Symptomatic pancreatitis and serum lipase > 5x ULN	Discontinue ponatinib
Myelosuppression	ANC < 1 x 10^9/L OR Platelets < 50 x 10^9/L	Interrupt ponatinib until ANC $\geq$ 1.5 x 10^9/L and platelets at least 75 x 10^9/L, then resume at the same dose If recurrence interrupt until resolution, then resume at next lower dose
Other non-hematologic adverse reactions	Grade 1	Interrupt ponatinib until resolved, then resume at same dose
	Grade 2	Interrupt ponatinib until Grade 0 or 1, then resume at same dose If recurrence, interrupt until Grade 0 or 1, and resume at next lower dose
	Grade 3 or 4	Interrupt until Grade 0 or 1, then resume at next lower dose Discontinue ponatinib if recurrence

ANC: absolute neutrophil count; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ULN: upper limit of normal