Ponatinib-Induced Adverse Effects: A Case Report
Thrombocytopenia, Pancreatitis, and Hepatotoxicity

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ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative disease that generates from malignant transformation of pluripotent hematopoietic stem cells. First line treatment for CML is the tyrosine kinase inhibitor (TKI), imatinib. For patients resistant or intolerant to imatinib, other TKIs, dasatinib, nilotinib, and ponatinib, are approved treatments. Patients who are resistant or intolerant to other agents are started on ponatinib as a last line option. Common adverse events of ponatinib are hypertension, dry skin, rash, abdominal pain, constipation, and nausea. More serious adverse effects include cardiovascular effects, fluid retention, pancreatitis, severe myelosuppression, and hepatotoxicity. Treatment for these adverse effects can include interrupting ponatinib therapy and providing symptomatic and supportive care. Reintroduction of agent can be considered when the serious event has resolved or the potential benefit of resuming therapy is judged to outweigh the risk. The patient is a 65 year old Caucasian male with a history of imatinib-resistant CML. The patient was started on ponatinib 45mg approximately 3 months prior to presentation after failure of previous regimens. He requires platelet transfusions for ponatinib associated thrombocytopenia. He presents with 4 days of new right flank pain with radiation to his right groin. Evidence of pancreatitis was found on endoscopic retrograde cholangiopancreatography (ERCP). LFTs were elevated on admission. The patient had no history of alcohol or steroid use. Ponatinib was discontinued on admission and within three days the patient's symptoms of thrombocytopenia, pancreatitis and hepatotoxicity began to resolve. After complete resolution of the pancreatitis, the patient was restarted on ponatanib 15mg as an outpatient. Patients started on ponatinib should have their serum lipase, amylase, liver enzymes, and platelets checked every 2 weeks for the first 2 months and then monthly. By checking levels regularly it may allow the physicians to decrease the dose before complications arise that may require hospitalization. Signs and symptoms of pancreatitis should also be monitored and started on a low dose to avoid complications.

HISTORY OF PRESENT ILLNESS

TP (the patient), a 65 year old Caucasian male, presented to the emergency department (ED) on 6/3 with 4 days of right flank pain with radiation to his right groin. His pain was variable in severity with no associated nausea, vomiting, constipation, or diarrhea. In the ED, TP was also found to have thrombocytopenia and anemia, with platelet count of 6,000/µL, Hgb 12.3g/dL, and Hct 35.9%. TP displayed no symptoms of overt bleeding. Elevated transaminases were also found on admission; AST was 284 IU/L, ALT was 185 IU/L with no evidence of jaundice or liver failure.

Past medical history: Imatinib-resistant CML, platelet transfusion dependent thrombocytopenia, bilateral non-obstructing nephrolithiasis, GERD, chronic anemia, hypertension, tubular adenoma, marijuana and tobacco use (52 pack year history; quit 1/2013; currently uses electronic cigarettes)

Medications prior to admission:

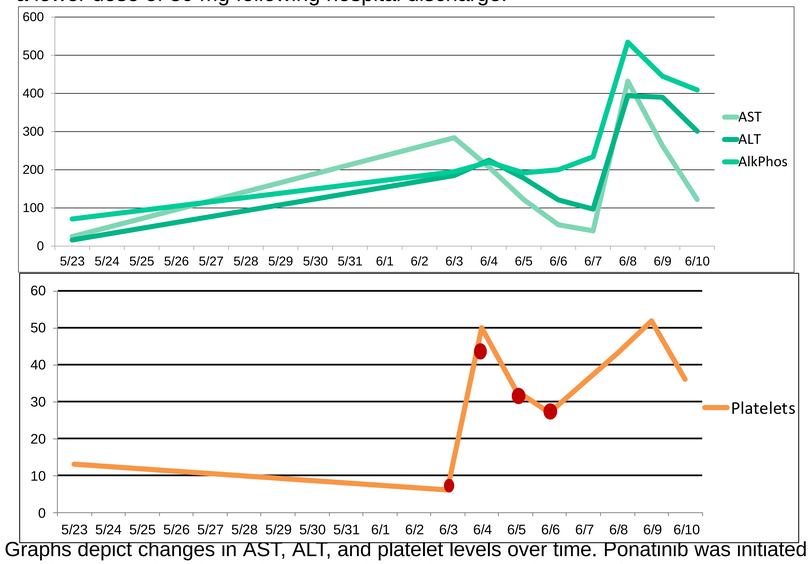
- Tramadol 50 mg PO TID for pain
- Ponatinib 45 mg PO daily for CML
- Ondansetron 8 mg PO BID prn N
- Docusate NA 100 mg PO BID
- Dronabinol 5 mg PO BID ac
- Hydrocodone/APAP 5/500 mg PO Q6H prn pain
- Ammonium Lactate 12% lotion to skin BID for dry skin
- Amlodipine 5 mg PO daily for HTN
- Sinus Rinse 1 packet nasally BID prn
- PEG 3350 1 TBSP daily mixed in 8 oz of water, juice, soda or coffee
- Fluticasone 50 mcg spray once in each nostril daily

CASE REPORT

In the ED (6/3/13), medications used for symptom relief included:

- PEG 3350 1 TBSP PO
- Ammonium Lactate 12% lotion to skin
- Docusate 100mg PO
- Fluticasone 50 mcg in each nostril
- Ondansetron 4 mg IV x 3 doses
- Pantoprazole 40 mg PO x 2 doses
- Tramadol 50 mg PO x 4 doses

Due to low platelet count in ED (6,000 platelets/µL) and elevated transaminases, ponatinib was held. A computed tomography (CT) scan showed an increase in intra and extrahepatic ducts, common duct, and pancreatic ducts extending to the ampulla. After an ERCP, evidence of acute pancreatitis was found. Ponatinib was discontinued on admission (6/4/13), and pancreatitis resolved. Platelet transfusions were given until platelet count increased. Ponatinib was restarted at a lower dose of 30 mg following hospital discharge.



Graphs depict changes in AST, ALT, and platelet levels over time. Ponatinib was initiated on 2/13, discontinued 6/4 after presenting to the ED, and resumed at a lower dose on 6/8. Due to the drop in platelet count (6/9) and rise in LFTs, ponatinib was discontinued again and restarted on 6/14/13. Platelet transfusions (●) were administered until platelets were ≥ 25,000 for ERCP.

ANALYSIS OF THE REACTION

Use of the Naranjo adverse drug reaction probability scale[1,2] indicated a probable relationship with thrombocytopenia (score of 8) and elevated transaminases (score of 7). The scale assigned a possible relationship with pancreatitis (score of 4) and ponatinib in this patient. While the Naranjo scale[1] only found a possible-probable relationship with the adverse events, they were likely to be drug induced. Other causes of the adverse effects were considered and excluded. Patient was not taking any other medications that could cause pancreatitis, thrombocytopenia and/or elevated transaminases and he had no history of alcohol or steroid use. ERCP ruled out cancer and granuloma. Pancreatitis resolved upon discontinuation of ponatinib, so galls stones as a cause was ruled out.

SEVERITY

The adverse effects were severe. The patient was admitted due to pain, thrombocytopenia and elevated transaminases. He required daily monitoring for bleeding, fever and pain. He required daily platelet transfusions and hydration until ERCP could be performed. Due to the need for an ERCP procedure, the patient spent additional time in the hospital.

OUTCOMES

After ponatinib discontinuation, and the administration of fluid replacement and blood transfusions, transaminases, platelets and symptoms of pancreatitis normalized. Following hospital admission, the patient was restarted on a decreased dose of 15 mg daily which was increased after a week to 30 mg. After re-initiation, there were no signs of pancreatitis or elevated transaminases. Due to low platelet count (33,000 platelets/µL), ponatinib therapy was again discontinued the following month. When platelet count increased again, the patient was restarted on 15 mg daily. Ponatinib was eventually discontinued due to lack of efficacy and bosutinib was initiatied.

DISCUSSION

For patients who are resistant or intolerant to imatinib, dasatinib, or nasatinib, physicians could initiate ponatinib. Patients started on CML treatment are routinely monitored for thrombocytopenia and myelosuppression. Myelosuppresion typically occurs within the first 4 weeks of therapy and is more common in patients with advanced disease.[3] In the 43 patients with chronic phase CML, treatment-related thrombocytopenia of grade 3 or more occurred in 12 patients (28%).[2]

Ponatinib can also cause acute pancreatitis and liver dysfunction. Dose-limiting toxic effects included pancreatic events, with pancreatitis observed in 14% of patients. Patients should be educated and monitored on signs and symptoms of pancreatitis. Cortes et. al discussed that thrombocytopenia and pancreatic are self-limiting once the drug is discontinued.[2] Discontinuation of ponatinib should resolve pancreatitis symptoms within 2 weeks.[2] There is no research evaluating restarting the medication. However, it is recommended to decrease the dose and serum lipase levels should be checked every 2 weeks for the first 2 months of initiation, and then monthly thereafter.[3] For patients with history of alcohol abuse, additional serum monitoring should be considered.[4] This case showed that discontinuation of ponatinb allowed the patient's labs to normalize. Due to lack of an available alternative agent, the patient was restarted on ponatinib until patient eventually failed therapy.

On October 31st, Ariad Pharmaceuticals suspended production of ponatinib due to case reports of life-threatening blood clots and severe narrowing of blood vessels linking the drug to fatal heart attacks and strokes within two weeks of initiation.[5] Ponatinib can only be requested for compassionate use in U.S. however, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency have decided to keep ponatinib on the market with a stronger warning precautions.[6]

REFERENCES & DISCLOSURES

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Saba Hasan, Crystal Fedorkiv and Naba Rahman- nothing to disclose
Jennifer Andres – nothing to disclose