Three Cases of Neutropenic Enterocolitis Following Midostaurin Administration
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Introduction
Neutropenic enterocolitis is defined as inflammation of the lower GI tract, classically called typhlitis when the cecum is involved, seen at times of severe neutropenia. It is most commonly associated with the use of cytotoxic chemotherapeutic medications but other risk factors include prolonged antibiotic or steroid use, myeloproliferative disorders, or significant cecal distension with mucosal injury.

Midostaurin is a small-molecule inhibitor of the FMS Tyrosine Kinase–Like receptor (either internal tandem duplication or tyrosine kinase domain mutations) seen in some variants of acute myeloid leukemia (AML). This medication was approved for treatment of patient with AML with FLT3 ITD or TKD positive AML in April of 2017 along with standard chemotherapeutic regimens.

Methods and Common Features
Case information was gathered by review of relevant patient records from cases at our facility.

All three cases were patients with newly diagnosed AML with FLT3 mutations. They were all started on standard chemotherapeutic regimens in the 7+3 treatment plan (2 with cytarabine and daunorubicin, 1 with cytarabine and idarubicin). Midostaurin was started on day 8 of therapy and was to be continued until day 21 per protocol in the RATIFY trial. All patients were initiated on appropriate prophylactic medications at or before onset of neutropenia.

Cases
Case 1 is a 59 year-old male who developed pruritic rash and abdominal pain 2 days after starting midostaurin. CT scan on day 13 showed typhlitis and patient developed neutropenic fever. Midostaurin was held and antibiotics were escalated. Symptoms improved and midostaurin was restarted on day 21 and held again on day 22 after recurrence of symptoms.

Case 2 is a 35 year-old female who was febrile at admission with negative workup who developed fever, rash, and abdominal pain 2 days after midostaurin initiation. CT showed inflammation of ascending colon and cecum and midostaurin was held. It was restarted on day 14 after improvement of symptoms but withdrawn again on day 18 due to recurrence of symptoms.

Case 3 is a 73 year-old female who developed rash, fevers, and abdominal pain on the second day of midostaurin therapy. Antibiotics were escalated and CT showed inflammation of the rectosigmoid colon and cecum. Patient continued midostaurin and blood cultures grew vancomycin-resistant Enterococcus for which she completed therapy. Patient completed course of midostaurin with symptomatic treatment for rash and diarrhea.

Discussion
Midostaurin is a new therapeutic option for a specific variety of AML. At this time, while it has passed through Phase III clinical trials, not much is known regarding its side effect profile. Stone et al. discussed the increased likelihood of gastrointestinal side effects after midostaurin introduction but these side effects were less severe and included nausea and vomiting. No previous link between midostaurin administration and the development of neutropenic enterocolitis has been established.

Conclusion
Our cases provide three examples where midostaurin initiation appears to have precipitated enterocolitis in patients who were neutropenic. While neutropenic enterocolitis has been reported with cytotoxic chemotherapeutic agents like those used in the regimens for these patients, the development of symptoms correlated with midostaurin induction and resolved after its removal.

References