Recurrent Hyperbilirubinemia with Midostaurin during Consolidation in a Patient of AML with FLT3 Mutation and Review of Literature for Alternative Maintenance Strategy

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Abstract

Midostaurin-induced hyperbilirubinemia during consolidation chemotherapy is uncommon. Dose-modification strategy for midostaurin in presence of hyperbilirubinemia remains undefined. We report a case of a young woman diagnosed as acute myeloid leukemia having normal cytogenetics with FLT3-ITD (internal tandem duplication) mutation who tolerated midostaurin during induction but developed recurrent hyperbilirubinemia without transaminitis with midostaurin during high-dose cytarabine consolidation. The pattern of hyperbilirubinemia with midostaurin was transient and rapidly reversible on stopping the drug, but recurred thrice. Sanger sequencing for UGT1A1*28 polymorphism failed to detect relevant variations. In the absence of any other approved FLT3 inhibitor in first line setting, she received sorafenib maintenance at 200 mg twice daily in combination with subcutaneous azacitidine. The combination was well tolerated without hyperbilirubinemia with sorafenib.

Keywords
- AML
- FLT3 mutation
- midostaurin
- hyperbilirubinemia
- sorafenib

Key Message:

Safety of sorafenib in the setting of recurrent hyperbilirubinemia with midostaurin is not known. In this case report the combination of sorafenib with parenteral azacitidine was well tolerated without recurrence of hyperbilirubinemia.

Introduction

Acute myeloid leukemia (AML) treatment has rapidly evolved in last 3 to 4 years with the approval of newer molecularly directed therapies. Midostaurin was first in the class of FLT3 inhibitor that was approved in the treatment of patients with AML having FLT3 mutations.

Newer FLT3 inhibitors approved or being studied in relapse refractory AML patients with FLT3 mutation include gilteritinib, quizartinib, and crenolanib.[1] The IDH1 inhibitor ivosidenib and IDH2 inhibitor enasidenib are Food and Drug Administration approved in patients with relapse refractory AML. The newer agents both mutation specific and nonspecific

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have improved outcomes of patients with AML, but managing adverse effects of these new drugs is also a challenge.[2]

Present case discusses a rare adverse effect of recurrent hyperbilirubinemia with midostaurin during consolidation chemotherapy, leading to the discontinuation of the drug. Patient tolerated a different FLT3 inhibitor sorafenib without recurrent hyperbilirubinemia.

Case Report

A 37-year-old female with no comorbid illness presented with fever and persistent cough of 10 days duration. With complete blood count showing hemoglobin = 8.5 gm/dL, white blood cell = 149,680 cells/mm^3, platelet = 23,000/mcl, and with a suspected diagnosis of acute leukemia, she was referred to us. Peripheral smear suggested 97% blasts of moderate to large size with moderate cytoplasm that were myeloperoxidase (MPO) positive, suggestive of AML. She was started on hydroxyurea and posaconazole prophylaxis. Flow cytometry and initial molecular workup confirmed the diagnosis of AML.

She received 3 days daunorubicin and 5 days cytarabine as induction. A decision to omit last 2 days of cytarabine infusion was made in view of clinically and radiologically worsening fungal pneumonitis despite appropriate antifungal treatment.

FLT-3 gene ITD analysis was positive and the mutant allele ratio (AR) was 0.23. She was started on innovator brand of midostaurin at 50 mg twice daily from day +8 with electrocardiogram, blood sugar, and liver function test (LFT) monitoring. She had asymptomatic grade 2 transaminitis during midostaurin administration, so the drug was continued with careful monitoring. She received platelet, blood, and granulocyte transfusion appropriately. Supportive care with intravenous antibiotics and liposomal amphotericin was continued. Next-generation sequencing panel showed presence of IDH2 mutation in addition to FLT-3 and NPM1 mutations, while cytogenetics showed scanty metaphases with poor morphology with normal karyotype. She belonged to European LeukemiaNet (ELN) favorable risk group.

Disease evaluation on day +28 showed bone marrow in morphological remission. Measurable residual disease (MRD) assessment by flow cytometry was positive, while MRD for molecular markers could not be done because of logistics of transporting sample to appropriate laboratory due to ongoing coronavirus disease-2019 (COVID-19) pandemic.

She was started on high-dose cytarabine (HIDAC) consolidation at 3 gm/m^2 twice daily given on days +1, +3, and +5. Posaconazole was started as antifungal prophylaxis from day +1 but on day +5 in view of persistent transaminitis it was stopped and instead liposomal amphotericin was started as prophylaxis during present and subsequent consolidation cycles after infectious disease specialist consultation. LFT on day +8 showed grade 3 transaminitis, but bilirubin was normal. Midostaurin was started on day +8 at 50 mg twice daily, with planned serial LFT monitoring. Midostaurin was omitted from day +11 to +14 in view of persistent nausea and vomiting despite optimal antiemetic treatment, but LFT showed decreasing transaminitis. On day +15 after improvement in nausea and vomiting midostaurin was restarted; at this time point LFT was normal. But on day +17 she was icteric and LFT suggested grade 3 hyperbilirubinemia without transaminitis. Abdominal ultrasound was normal. Repeat viral markers including hepatitis B surface antigen and hepatitis C virus were negative. Drug chart of patient was reviewed for potential drugs causing hepatotoxicity and a decision to stop midostaurin was made. LFT trend during first-cycle consolidation is shown in ►**Table 1**.

After first-cycle consolidation, MRD from bone marrow by flow cytometry was negative. MRD was also negative for FLT-3 gene mutation and NPM1 gene mutation. She had 10/10 human leukocyte antigens (HLA) matched sibling donor available, so option of consolidation with matched sibling allogenic transplant was discussed with patient and family. A decision to continue HIDAC was made by the family.

She received second-cycle HIDAC as per previous schedule and innovator brand of midostaurin was started from day +8 at 50 mg twice daily with appropriate monitoring. On day +17 she developed high colored urine but with the history of hyperbilirubinemia due to midostaurin during last consolidation, the drug was stopped, at grade 2 hyperbilirubinemia. LFT trend during second-cycle consolidation is shown in ►**Table 1**.

She received third-cycle HIDAC as per previous schedule and though patient had transient grade 2 to 3 hyperbilirubinemia twice with midostaurin, the decision to give it once more was taken after discussing pros and cons with the family. Innovator brand of midostaurin was started from day +8. She developed fever, rigors, vomiting, and hypotension on day +14. Blood investigations showed hyperbilirubinemia and acute kidney injury (AKI). Midostaurin was stopped and empirical antibiotics and supportive care were started. LFT trend during third-cycle consolidation is shown in ►**Table 1**.

Strategy of giving midostaurin alone in maintenance phase where confounding factors could have been removed was considered, but not tried as we and family considered it to be high risk as hepatotoxicity was recurrent and the last one was complicated with severe sepsis. Sanger sequencing for UGT1A1*28 polymorphism failed to detect relevant variations.

The fourth-cycle HIDAC was not given in view of poor tolerance to chemotherapy and also keeping in mind the recommendations from various guidelines to reduce the number of consolidation cycles to three in view of ongoing COVID-19 pandemic. We decided to give maintenance with subcutaneous azacitidine 75 mg/m^2 from day +1 to day +7 and sorafenib at 200 mg twice daily every 28 days for 1 year. She completed 12 cycles of azacitidine and sorafenib without any major toxicity and continues to be in remission.

Discussion

FLT3 gene mutation is seen in about 30% patients with newly diagnosed AML, and it is the most frequent molecular abnormality seen in AML.[3] FLT3 gene mutation is associated with increased risk of relapse and shorter overall survival.[4]

Table 1 LFT trends during first-, second-, and third-cycle HIDAC and midostaurin[a]

Day +1 from first-day HIDAC	Bilirubin (mg/dL): Total/Direct/Indirect	SGOT (IU/L)	SGPT (IU/L)	Intervention
+5	0.68/0.47/0.21	117	214	Posaconazole; stopped due to grade 3 transaminitis
+8	0.59/0.39/0.2	113	224	Midostaurin; started and given for 2 days
+14	0.87/0.75/0.12	10	32	Midostaurin; restarted next day (day +15)[a]
+17	5.46/5.32/0.14	32	54	Midostaurin; stopped
+18	2.17/2.02/0.15	14	40	Midostaurin; stopped
+19	1.43/1.32/0.11	29	54	Midostaurin; omitted
Day +1 from first day of second-cycle HIDAC	**Bilirubin (mg/dL): Total/Direct/Indirect**	**SGOT (IU/L)**	**SGPT (IU/L)**	**Intervention**
+9	0.81/0.37/0.44	29	42	Midostaurin; continued
+11 High colored urine	1.49/1.05/0.44	22	36	Midostaurin; stopped
+12	0.88/0.65/0.23	12	25	Midostaurin; omitted
Day +1 from start of third-cycle HIDAC	**Bilirubin (mg/dL): Total/Direct/Indirect**	**SGOT (IU/L)**	**SGPT (IU/L)**	**Intervention**
+14	0.65/0.37/0.28	22	46	Midostaurin; continued
+15 (morning)	4.19/1.87/2.32	26	43	Midostaurin; stopped
+15 (evening)	5.65/4.97/0.68	21	41	Midostaurin; stopped
+16	2.24/1.78/0.46	20	38	Midostaurin; omitted

Abbreviations: HIDAC, high-dose cytarabine; LFT, liver function test; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

[a]In cycle 1, midostaurin started from day +8 (day +1 counted from the start of HIDAC infusion) and it was given till day +10. The drug was stopped from day +11 up to day +14 due to intractable nausea and vomiting and restarted from day +15.

Midostaurin has been approved in treatment of AML based on the results of RATIFY trial.[5] The beneficial effect of midostaurin is seen in all four distinct FLT3-ITD genotypes based on the high or low mutant AR and presence or absence of NPM1 mutation based on a retrospective analysis[6] of RATIFY trial.

The phase 3 RATIFY trial[5] has reported an incidence of grade 3 or higher hepatotoxicity of 7%, which was comparable to placebo arm of the trial. There is no established dose-modification strategy for midostaurin in presence of hepatotoxicity.

In this case report the patient did not have hyperbilirubinemia during induction, but had hyperbilirubinemia without transaminitis thrice during HIDAC consolidation, typically from day +8 to day +10 after starting the drug.

It is difficult to explain why she did not have hyperbilirubinemia during induction, but developed it during consolidation. One of the possible explanations could be idiosyncratic drug reaction (IDR) due to midostaurin. One of the characteristics that are common to most IDRs is a delay between starting the drug and onset of symptoms.[7] IDRs that involve liver or bone marrow typically occur after 1 to 2 months. It is often difficult to attribute a single drug to an adverse effect when given with other hepatotoxic drugs like HIDAC, posaconazole, and other complicating factors like sepsis, but the occurrence of hyperbilirubinemia thrice, which resolved rapidly in 24 to 48 hours after stopping midostaurin, makes alternate cause of hyperbilirubinemia unlikely.

Hyperbilirubinemia with midostaurin as seen in the present case report is rare, as even in the RADIUS-X,[8] an expanded excess program of midostaurin to understand safety and tolerability of drug, no case of hyperbilirubinemia with midostaurin was noted during consolidation chemotherapy.

Strong CYP3A4 inhibitors when used concurrently with midostaurin can increase its drug levels.[9] In this case, posaconazole was stopped during first-cycle consolidation chemotherapy, in view of transaminitis, and it was not given concurrently with midostaurin. Drug interaction leading to increase in midostaurin level was not the cause of hyperbilirubinemia in this patient.

The genetic variations of UGT1A1, OATP1B1, and MRP2, whose protein-products are required for bilirubin metabolism and excretion, may be the predisposing factors for hyperbilirubinemia in the present case.[10] Sanger sequencing for UGT1A1*28 polymorphism in the present case failed to detect relevant variations. OATP1B1 and MRP2 genetic variations were not analyzed in the present case.

Consolidation with allogeneic stem cell transplant is preferred post remission treatment for patients with an estimated relapse risk exceeding 35 to 40%.[11] Consolidation with allogeneic stem cell transplant is an option for the patients with FLT3 AML in first remission irrespective of allelic ratio, particularly when a matched sibling donor is available.[12,13] The co-mutations along with FLT3 AML are

further helpful in risk stratification in AML. Family opted against consolidation allogeneic transplant. The option of surveillance alone after consolidation HIDAC was also possible, as the patient was intolerant to midostaurin and absence of any other approved maintenance approach. The decision to give azacitidine and sorafenib maintenance was made as she was young but clinically at higher risk of relapse. The increased risk of relapse was presumed because she had received less than recommended cytarabine dose during induction; also, midostaurin could not be given as per the approved schedule.

The maintenance strategy in AML has been tried for over last four decades, but the results have been suboptimal.[14] The absolute benefit of using midostaurin during maintenance in terms of prolongation of overall survival is unclear.[15] Recent ELN guidelines also suggest to continue midostaurin maintenance as per the registrational clinical trial, however acknowledging the lack of data supporting the absolute benefit added by maintenance midostaurin.[16] Recently another FLT3 inhibitor quizartinib was compared to placebo in combination with intensive chemotherapy induction and consolidation followed by maintenance for 3 years and showed improvement in overall survival.[17]

Parenteral azacitidine as a maintenance strategy in elderly AML has been studied in HOVON97 trial and it has shown improvement in disease-free survival.[18]

The National Cancer Research Institute (NCRI) UK AML-16 trial showed a benefit of parenteral azacitidine maintenance in improving overall survival in a subset of patients who were MRD negative after chemotherapy.[19,20] Also, oral azacitidine maintenance has shown to improve overall survival and relapse-free survival in patients over the age of 55 years with intermediate- and high-risk AML who have achieved remission after induction chemotherapy and are deemed unfit for transplant.[21] We did not consider use of oral azacitidine as the drug was unavailable in our country while managing this patient.

Venetoclax is a BCL-2 inhibitor that has shown to improve outcome of elderly patients unfit for intensive treatment in combination with azacitidine.[22] The combination has also shown benefit in case reports as induction treatment in young patients unfit for intensive induction.[23] Venetoclax has also been studied in combination with azacitidine in maintenance setting, but definitive phase 3 data are unavailable at present.[24,25]

Sorafenib is used off label in AML for upfront, maintenance, and relapse treatment with or without chemotherapy. The drug has four times higher in vitro FLT3-ITD inhibitory activity as compared to midostaurin.[26]

Sorafenib has been compared to placebo in the study Alliance Leukaemia trial[27] done in elderly AML patients unselected for molecular marker, in combination with $7+3$ induction and with consolidation cytarabine followed by up to 1-year maintenance sorafenib or placebo. The trial had less than 15% ($N=15$ in sorafenib arm) patients with FLT-3-ITD mutation. This trial failed to improve event free survival in the whole population.

The German randomized phase 2 trial SORAML[28] compared sorafenib 400 mg twice daily with placebo in young patients ($N=267$) between ages 18 and 60 years, in combination with 2 cycles of $7+3$ induction followed by 3 cycles of HIDAC followed by maintenance. There were 17% patients with FLT3 mutation in each arm; in this subset there was no improvement in event free survival, but there was a trend toward improvement in relapse-free survival and overall survival. In the overall population, the trial showed improvement in event free survival.

A retrospective study[29] has shown prolongation of event-free survival and overall survival irrespective of the use of allogenic transplantation in patients with AML with FLT3 mutation with use of sorafenib in combination with chemotherapy and as maintenance.

The approved dose of sorafenib in solid tumors like hepatocellular cancer and renal cell carcinoma is 400 mg twice daily. This approved dose of sorafenib is poorly tolerated because of mucositis, gastrointestinal toxicity, and hand foot syndrome. There is preclinical data showing that dose of 200 mg twice daily is equally effective as compared to standard dose.[30]

Conclusion

1. This case discusses pattern of recurrent reversible transient hyperbilirubinemia with midostaurin during consolidation with HIDAC, which was not seen during induction.
2. Sanger sequencing for UGT1A1*28 polymorphism in the present case failed to detect any abnormality. We were unable to identify the reason for hyperbilirubinemia with midostaurin in the present case.
3. The OATP1B1 and MRP2 genetic variations were not analyzed in the present case.
4. No approved dose-modification strategy of midostaurin in presence of recurrent hyperbilirubinemia exists.
5. Safety of sorafenib in the setting of recurrent hyperbilirubinemia with midostaurin is not known. In this case report the combination of sorafenib with parenteral azacitidine was well tolerated, without recurrence of hyperbilirubinemia.

Authors' Contributions

D.S. was involved in conceptualization, methodology, and writing.
S.K. was involved in supervision and writing.
R.P. helped in data curation and editing.

Patient's Consent

Written informed consent was taken from patient for publishing the case report.

Conflict of Interest

None declared.

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