GIST in Pregnancy: The Role of Circulating Tumor DNA to Define the Assessment of Risk of Rapid Progression and Response to Imatinib

Vaia Florou, MD; Jeremy Ramdial, MD; and Jonathan C. Trent, MD, PhD

Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Although the median age at the time of diagnosis is 60 years, GIST rarely arises in younger individuals. GIST during pregnancy is rare and few cases are reported in the literature. The mainstay of treatment of localized GISTs is surgical resection and, in unresectable/metastatic tumors, targeted tyrosine kinase inhibitors (TKIs), with significant improvement in overall survival. The management of newly diagnosed GIST in pregnancy is challenging. With limited safety data on TKIs in pregnancy, early termination of pregnancy has been advised. However, there is growing evidence in the literature of gravida patients treated with TKIs with uneventful outcomes. Here, we report a case of a young pregnant patient who was diagnosed with metastatic GIST in the second trimester and was treated with both surgical resection and a TKI (imatinib) due to the unique characteristics of her tumor. Both the patient and the fetus had favorable survival outcomes.

AJHO. 2017;13(11):37-40

Introduction

Gastrointestinal stromal tumors (GISTs) were among the first solid tumors for which highly effective, targeted therapy became available. In most GISTs, the KIT / PDGFRA pathways are activated by mutations in the respective genes.[1,2] The mainstay of treatment for unresectable disease is tyrosine kinase inhibitor (TKI) abrogation of the receptor and of downstream signaling pathways. Due to the rarity of this disease in the younger population, cases of GIST diagnosed during pregnancy have been scarcely reported. The most common treatment modality for these patients, as described in published cases, was surgical excision for symptomatic lesions; TKIs were usually initiated postpartum.[3-5] Treatment guidelines have not established a standardized approach in this setting, and data on the safety of TKIs are mainly derived from the experiences of patients who have chronic myeloid leukemia (CML).

Case Description

A 32-year-old gravida woman (pregnant for the first time and has not delivered) with an unremarkable medical history presented at a community hospital's emergency department (ED) with left upper quadrant pain accompanied by cough. She was in her 16th week of gestation when she first developed symptoms. Due to the persistence of pain and cough at 21 weeks of gestation, she sought medical care at the ED.

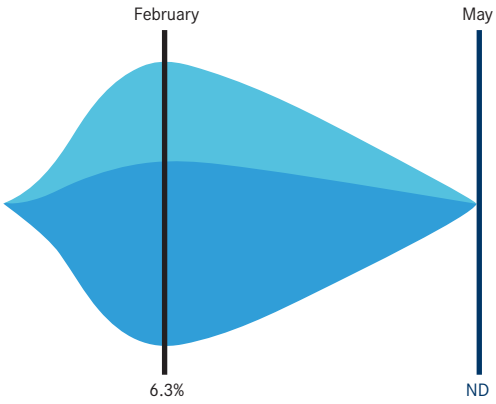
Abdominal imaging revealed a mass (21.4 × 11.1 × 16.3 cm) arising from the gastric fundus, with splenic invasion, ascites, and multiple liver lesions consistent with metastatic disease. Due to worsening abdominal pain, she underwent an exploratory laparotomy, with partial gastrectomy and splenectomy with resection of the tumor and liver nodule biopsy. Unfortunately, capsule rupture occurred intraoperatively and the tumor was resected piecemeal with positive margins. Upon pathology review, the mass and the liver lesion were proven to be a GIST with 37 of 50 mitoses per high-power field.

Due to postoperative complications of esophageal leak and enterocutaneous fistula, the patient was transferred to a sarcoma center; there, she was managed by specialists in GIST and maternal-fetal medicine. Circulating tumor DNA obtained at that time revealed the presence of *c-KIT* exon 11 mutation at amino acids W557 and K558 (6.3% of total circulating DNA). Given the high-grade nature of her GIST, and the high tumor proliferation rate in tumors with these particular amino acid deletions, imatinib was initiated at 26 weeks of gestation (**Figure 1**). The starting dose was 100 mg daily, and it was escalated every 4 days to a final dose of 400 mg per day. Overall, she tolerated the medication well,

other than a transient elevation of aspartate transaminase (AST) and alanine transaminase (ALT) 1 week into the 400-mg dose. This required a temporary 1-day cessation of the medication, after which liver enzymes normalized.

At 29 weeks of gestation, the patient experienced preterm premature rupture of membranes; the imatinib was held in preparation for caesarean section. She delivered a preterm underweight baby boy, and imatinib was restarted at 400 mg 6 days postpartum. A computed tomography scan of the abdomen post partum showed hepatomegaly with multiple enhancing lesions (**Figure 2**). She was discharged home in stable condition. She was evaluated in a GIST clinic 1 month later, where she was found to be tolerating imatinib 400 mg per day with AST/ALT within normal limits. Two months after the delivery, repeat imaging showed stable disease in the liver with hypoattenuating liver lesions and no new lesions. Repeat circulating tumor DNA testing could not detect any DNA encoding mutation in *KIT* (Figure 2). Imaging of the chest showed no evidence of metastatic disease. Her son was discharged from the neonatal intensive care unit approximately 2 months after delivery in stable health.

FIGURE 1. The Decrease of c-*KIT* Exon 11 Mutation From 6.3% of Total Circulating DNA to Nondetectable (ND)



ND indicates non detectable

Discussion

GISTs are the most common gastrointestinal mesenchymal tumors, but their overall incidence is rare, with fewer than 10 cases per 1 million persons diagnosed every year in the United States.[6-8] The mean age of patients diagnosed with GIST is 62.9 years, and men are affected 1.5-fold more than women.[7] Thus, the incidence of GIST in pregnancy is extremely rare, with only a handful of case reports available in the literature. The management of such cases is challenging, requiring a multidisciplinary approach. In a recent review by Zarkavelis et al[3] of GIST cases diagnosed during pregnancy, the median gestational age at diagnosis was 18 weeks, which is consistent with our case.

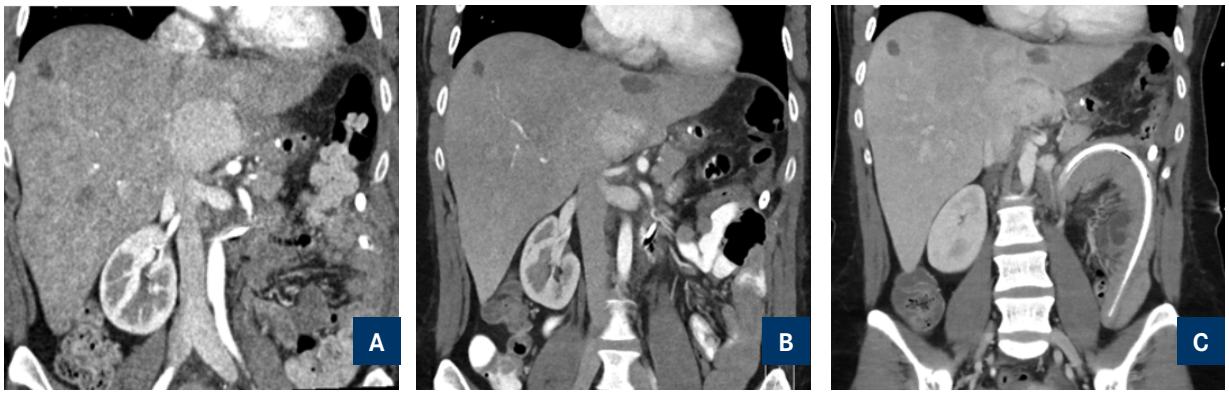
About 80% of all patients with GIST have tumors harboring gain-of-function mutations in the *KIT* proto-oncogene—exon 9, 11, 13, or 17.[1] It has been reported that 5% to 10% have mutations in the *PDGFRA* gene.[9] The standard therapeutic modality in localized/resectable GIST is surgical resection, but for metastatic disease, imatinib—a TKI with targeted activity against *KIT* and *PDGFRA*—is the mainstay of therapy. Adjuvant treatment following surgical resection depends on the calculated risk of recurrence based on tumor size, location, mitotic index, and capsule violation during surgery. In our case, the patient was diagnosed with metastatic disease at diagnosis. Imatinib was shown to be teratogenic in preclinical studies in rats but not rabbits, and data in humans are lacking. It appears to cross the placenta poorly, as often happens with drugs bound to plasma proteins or of high molecular weight.[10]

Much of the data available regarding the safety of imatinib during pregnancy come from studies on patients with CML in whom imatinib is also used due to its targeted activity on the BCR-ABL oncogene. One of the largest case series on outcomes of pregnant patients with CML treated with imatinib, published by Pye et al,[11] included 180 pregnant women. Despite the lack of pregnancy outcome data in 55 of the 180, this study showed that a significant number of patients (50%) had pregnancies that were uneventful for both the mother and the infant.

It has been reported that 28% had elective pregnancy termination and congenital defects were observed in the babies of 12 patients, with the majority of those (10 of 12; 83%) being exposed to imatinib during the first trimester. The fetal malformations seen were defects of bone (skull and spine), kidney, and heart; exophthalmos; hydrocephalus; and heart and cerebellar hypoplasia. Notably, half of these patients were exposed to other medications during pregnancy, such as hydroxyurea, warfarin, and interferon.

Another important aspect of our patient's case was the presence of the specific amino acid deletions in exon 11 of *KIT* (W557 and K558), which underscored the need for imatinib during pregnancy. In patients with resected GISTs harboring the 557 and/or 558 codon deletions in exon 11, the metastatic propensity of these tumors is higher[12] and the progression-free survival (PFS) is lower when compared with patients

FIGURE 2. CT Scans of the Abdomen: Response of the Liver Lesions Over Time



Immediately after the caesarean section

Two months later

Three months later. Lesions are gradually becoming more necrotic

CT indicates computed tomography.

with other *KIT* mutations or wild type tumors pre-imatinib.[13] Nevertheless, GISTs with exon 11 in general have the highest sensitivity to imatinib and there is no difference in PFS and overall survival amongst the patients with deletions in codons 557 and 558 compared with other deletions when treated with imatinib.[14,15]

In pregnant patients with GIST, the risk of fetal complications, especially in the first trimester, may delay initiation of therapy with a TKI until antepartum. On the other hand, delay in imatinib therapy could put the mother at risk for progression and death.

Thus, the decision to initiate imatinib in the pregnant patient depends upon the predicted response to imatinib and the aggressiveness of the underlying tumor (size, anatomic location, mitotic rate, mutation, presence of metastases, and tumor rupture).

Conclusion

GISTs are rare tumors, and in pregnancy they are an even rarer occurrence. Initiation of treatment in gravida women should be individualized based on patient and tumor characteristics. There are insufficient data in the literature to conclude that imatinib is harmful to the unborn child after the first trimester of pregnancy. Patients treated with imatinib should in general use effective methods of contraception.

Despite being a report of a single positive outcome, this case highlights the possibility that if a patient conceives during therapy or if a patient needs to receive imatinib during pregnancy, the pregnancy may evolve uneventfully for both mother and child, especially when the TKI is introduced after the first trimester.

Author affiliations: All authors are with the Department of Medicine, Division of Hematology and Oncology, University of Miami, Miller School of Medicine, and Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, Florida.

Financial disclosures: Dr Trent reports participating in paid advisory boards and receiving consultation fees from Eli Lilly and Company, Eisai Co, and Janssen.

Address correspondence to: Vaia Florou, MD, 1475 NW 12th Ave, Suite 3300 (D8-4), Miami, FL 33136; Tel: 305-585-7409; E-mail: vaia.florou@jhsmiami.org.

References:

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science.* 1998;279(5350):577-580.

2. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science.* 2003;299(5607):708-710. doi: 10.1126/science.1079666.

3. Zarkavelis G, Petrakis D, Pavlidis N. Gastrointestinal stromal tumors during pregnancy: a systematic review of an uncommon but treatable malignancy. *Clin Transl Oncol.* 2015;17(10):757-762. doi: 10.1007/s12094-015-1315-x.

4. Valente PT, Fine BA, Parra C, Schroeder B. Gastric stromal tumor with peritoneal nodules in pregnancy: tumor spread or rare variant of diffuse leiomyomatosis. *Gynecol Oncol.* 1996;63(3):392-397. doi: 10.1006/gyno.1996.0342.

5. Scherjon S, Lam WF, Gelderblom H, Jansen FW. Gastrointestinal stromal tumor in pregnancy: a case report. *Case Rep Med.* 2009;2009:456402. doi: 10.1155/2009/456402.
6. Rubin JL, Sanon M, Taylor DC, et al. Epidemiology, survival, and costs of localized gastrointestinal stromal tumors. *Int J Gen Med.* 2011;4:121-130. doi: 10.2147/IJGM.S16090.
7. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol.* 2005;100(1):162-168. doi: 10.1111/j.1572-0241.2005.40709.x.
8. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev.* 2015;24(1):298-302. doi: 10.1158/1055-9965.EPI-14-1002.
9. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol.* 2005;23(23):5357-5364. doi: 10.1200/JCO.2005.14.068.
10. Russell M, Carpenter M, Akhtar M, et al. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. *J Perinatol.* 2007;27(4):241-243. doi: 10.1038/sj.jp.7211665.
11. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. *Blood.* 2008;111(12):5505-5508. doi: 10.1182/blood-2007-10-114900.
12. Wardelmann E, Losen I, Hans V, et al. Deletion of Trp-557 and Lys-558 in the juxtamembrane domain of the c-kit protooncogene is associated with metastatic behavior of gastrointestinal stromal tumors. *Int J Cancer.* 2003;106(6):887-895.
13. Martín J, Poveda A, Llombart-Bosch, et al; Spanish Group for Sarcoma Research. Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS) [published correction appears in *J Clin Oncol.* 2006;24(11):1784]. *J Clin Oncol.* 2005;23(25):6190-6198. doi: 10.1200/JCO.2005.19.554.
14. Bachet JB, Hostein I, Le Cesne A, et al. Prognosis and predictive value of KIT exon 11 deletion in GISTs. *Br J Cancer.* 2009;101(1):7-11. doi: 10.1038/sj.bjc.6605117.
15. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol.* 2003;21(23):4342-4349. doi: 10.1200/JCO.2003.04.190.