Neoadjuvant Imatinib for Borderline Resectable GIST

M. Zach Koontz, MD; Brendan M. Visser, MD; and Pamela L. Kunz, MD

Abstract

A 36-year-old woman presented to the emergency department with black stools and syncope. Her hemoglobin was 7.0 and her red blood cells were microcytic. Upper endoscopy did not identify a clear source of bleeding, but a bulge in the third portion of the duodenum was noted. A CT scan showed a large extraintestinal mass, and follow-up esophagogastroduodenoscopy/endoscopic ultrasound with biopsy revealed a spindle cell neoplasm, consistent with gastrointestinal stromal tumor (GIST). Because of the size of the lesion and association with the superior mesenteric vein and common bile duct, she was referred to medical oncology for consideration of neoadjuvant imatinib. Neoadjuvant tyrosine kinase inhibitor therapy for GISTs is emerging as a viable treatment strategy for borderline resectable tumors, although the dose, duration, and optimal imaging modalities have not been clearly established. Recent pathologic and radiographic data have provided insight into the mechanism and kinetics of this approach. This case report presents a patient for whom surgery was facilitated using neoadjuvant imatinib. (*JNCCN* 2012;10:1477–1482)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the rationale for the management methods used in this case presentation.
- Describe the ideal management of a patient with borderline resectable disease.

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Case Report

A 36-year-old woman with a past medical history significant for upper gastrointestinal bleeding of unclear source presented to her primary medical doctor complaining of abdominal fullness, early satiety, and fatigue. CBC, comprehensive metabolic panel, thyroid function studies, and C-reactive protein and tissue transglutaminase levels were normal. Her doctor recommended a CT scan, but the patient asked to be seen by her gastroenterologist, who recommended observation in the context of improving symptoms. Shortly thereafter she developed black stools with syncope and a CT scan was ordered, which revealed a 7.3 x 8.9 x 8.8 cm left upper quadrant mass. Esophagogastroduodenoscopy showed 2 nonbleeding linear erosions in the stomach with patchy erythema and a bulge in the third portion of the duodenum. Endoscopic ultrasound (EUS) further characterized the periduodenal mass as greater than 7 cm, heterogeneous, well-circumscribed, and extrinsic to the stomach, possibly arising from the small bowel. Elastography showed the mass to be firm with sporadic areas of lower density. Liver, pancreas, gall bladder, and celiac axis appeared uninvolved. EUS-guided fine-needle aspiration and core biopsies showed sheets of crowded but uniform spindled cells with elongated nuclei, variably prominent nucleoli, and delicate cytoplasm in a background of bland glandular epithelium. Immunohistochemical staining for CD117 and DOG1 was positive, supporting the diagnosis of gastrointestinal stromal tumor (GIST). Repeat CT was performed, which showed a 11.2 x 8.3 cm mass (Figure 1A) arising from duodenum, with compression of the superior mesenteric vein (SMV) and common bile duct (CBD). PET scan showed the mass to be hypermetabolic, with a maximum standardized uptake value (SUV) of 12 (Figure 1B). Because of the size and proximity to the SMV, the patient was referred for consideration of neoadjuvant imatinib with the hope of shrinking the tumor enough to facilitate duodenectomy rather than requiring a Whipple pancreaticoduodenectomy.

Her past medical and surgical history was significant for a complicated appendectomy requiring partial bowel resection, tonsillectomy, cesarean section, and unexplained previous gastrointestinal bleeding. She has a paternal uncle with a history of 2 synchronous colon cancers, but otherwise no cancers in the family.

On review of systems, she complained of mild fatigue and abdominal fullness occasionally associated with a dull ache in her abdomen. She had no further black stools, nausea, vomiting, or weight loss.

Imatinib was initiated at 400 mg daily. Four days later, she presented to the emergency department with nausea, vomiting, fevers, tachycardia, and an elevated WBC count. CT showed new gas within the tumor, consistent with liquefaction necrosis. She was treated with antibiotics and discharged on continued imatinib. A contrast CT after 3 weeks on therapy showed modest decrease in overall size of the tumor (Figure 1C), now measuring 9.1 x 6.6 cm, with improved effect on the SMV and CBD.

After 5 weeks of therapy, she developed fevers again, this time associated with parotid gland swelling, cough, and shortness of breath. CBC revealed elevated WBC levels with bandemia but absolute lymphopenia; laboratory values were otherwise normal. A chest radiograph showed diffuse bilateral reticular opacities. The patient was placed on broad-spectrum antibiotics. A CT of the thorax showed diffuse bilateral ground glass opacities and interlobular septal thickening. A bronchoscopy showed normal airways; lavage of the right middle lobe did not reveal an organism. Ultimately, the patient was believed to have a viral syndrome leading to parotitis and pneumonia, possibly related to imatinib. She was discharged on empiric antibiotics and experienced a full recovery. After a 1-week break in therapy, imatinib was restarted at the prior dose.

After 11 weeks of therapy, a surveillance PET revealed dramatic response to treatment; the mass measured approximately 7.7 x 5.4 cm and only showed minimal metabolic activity in a small central area, with a maximum SUV of 3.0 (Figure 1D). She then underwent resection of her tumor 3 weeks after discontinuing imatinib. Because of the location of the tumor and involvement of the SMV, a Whipple procedure was required. However, it was believed that the neoadjuvant imatinib made this procedure possible. Pathology revealed a GIST measuring 8 x 8 x 7.5 cm (Figure 2) with 9 mitoses per 50 high powered fields (HPFs), 0 of 15 lymph nodes were involved, and immunohistochemistry was positive for KIT and DOG-1. She recovered and is scheduled to receive 36 months of adjuvant imatinib.

Neoadjuvant Imatinib for GIST

Figure 1 A) CT with contrast before treatment showing tumor in largest cross-section 11.2 x 8.3 cm. B) PET scout image before treatment showing highly metabolically active primary tumor (arrow). C) CT with contrast after 3 weeks of imatinib showing modest decrease in size to 9.1 x 6.6 cm in similar cross-section. D) PET scout image after 11 weeks (arrow denotes left kidney, no residual tumor FDG activity).

Discussion

GISTs are mesenchymal tumors found primarily in the gastrointestinal tract. As a group, they are generally characterized by overexpression of KIT (CD117), and greater than 80% have an identifiable mutation that leads to constitutive activation of the KIT receptor.¹ Of the remaining KIT-negative tumors, a significant proportion express overactivation in the related receptor tyrosine kinase, platelet-derived growth factor receptor.² Factors predictive of tumor recurrence after resection include size, mitotic rate, and location of the primary tumor,³ and stratification into prognostic groups based on these is informative.⁴⁻⁶

The introduction of tyrosine kinase inhibitors in the treatment armamentarium for GISTs has brought significant improvements in outcomes.⁷ The approval of imatinib in the metastatic/advanced setting was

based on the phase II study by Demetri et al,⁸ which showed an overall response rate of 38%. Subsequent phase III trials have confirmed safety and efficacy in this setting, with similar response rates and time to progression between once- and twice-daily dosing, although with more grade 3 and 4 toxicities associated with the latter.^{9,10} Currently, the standard dose of 400 mg daily is recommended, with dose escalation to 800 mg for treatment failure.

Because of these successes in the advanced/metastatic setting, perioperative treatment has been explored. A large phase III trial examined the role of adjuvant imatinib versus placebo for 1 year after resection.¹¹ Imatinib significantly improved recurrence-free survival (99% vs. 83%; hazard ratio [HR], 0.35). Notably, one-quarter of these patients had tumors greater than 10 cm, and subset analysis showed that these high-risk patients derived the greatest

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Figure 2 A) Original resected specimen, anatomic configuration. B) Posterior view showing pancreas adherent to tumor.

benefit. Based on this result, imatinib was granted accelerated FDA approval in 2008 for the adjuvant treatment of KIT-positive GISTs. A subsequent study explored adjuvant treatment for 12 versus 36 months in resected GIST at high risk of recurrence (>10 cm, >10 mitoses/50 HPFs, >5 cm and >5 mitoses/50 HPFs, or tumor rupture). Superior recurrence-free and overall survival rates in the 36- versus 12-month treatment arms were reported (5-year recurrence free survival, 66% vs. 48%; $P<.0001$, and 5-year overall survival, 92% vs. 82%; $P=.019$).¹²

The role of imatinib in the treatment of GIST continues to evolve¹³ and data continue to emerge in the neoadjuvant setting, where it has been shown to be effective in both retrospective and prospective studies. In their retrospective review, Andtbacka et al¹⁴ describe 46 patients who were treated with imatinib for locally advanced primary or recurrent/meta-

static disease; all patients (11) in the former group and 31% (11/35) in the latter group underwent resection.

More evidence for this approach is shown in 2 separate prospective phase II trials. The first (RTOG 0132/ACRIN 6665) enrolled patients with primary GISTs 5 cm or greater or metastatic/recurrent tumors 2 cm or greater and treated them with 600 mg of imatinib for 8 to 12 weeks before resection. Most patients with primary tumors had stable disease (83%) by standard RECIST, a minority of patients had a partial response (7%), and no patients experienced progression. In this series, only 13% did not undergo resection. R0 resection was achieved in most (77%) patients with primary GISTs. Surgical complication rates were similar to those in historical controls, suggesting that treatment was safe (with most patients treated up to the day before surgery), and the estimated overall survival at 3 years was 84%.¹⁵ The low response rates in this study may be a function of declaring the appropriate imaging modality or response criteria. Choi et al¹⁶ proposed new response criteria for GIST: 10% decrease in maximal diameter or 15% decrease in density on CT imaging. This has been shown to correlate better with disease outcomes for GIST than standard RECIST.¹⁷

A second neoadjuvant study published by McAuliffe et al¹⁸ showed remarkable responses based on PET imaging. In this phase II study, 19 patients were randomized to receive 600 mg of imatinib preoperatively for 3, 5, or 7 days followed by postoperative imatinib for 2 years. The primary end point was tumor apoptosis, and correlations were made to radiographic responses. PET responses were defined as absolute SUV of 3.9 or less or 40% reduction, and dynamic CT was used to assess tumor blood flow. As in the study by Eisenberg et al,¹⁵ preoperative imatinib seemed to be well tolerated and safe. Radiographic responses (PET and/or dynamic CT), as defined by the authors, were seen in all patients, but a correlation with pathologic tumor response (apoptosis) was not observed. At median follow-up of 32 months, disease-free survival was 87%. This evidence of early response as assessed by alternative imaging modalities to standard RECIST is exciting, especially in the context of early studies reporting more than 3 months before partial response as defined by standard RECIST criteria.⁸

The optimal length of neoadjuvant therapy is unknown. The RTOG/ACRIN investigators chose 8

to 12 weeks largely based on median time to partial response (2.7 months) in the metastatic setting.⁸ In a retrospective analysis of the BFR14 trial,¹⁹ which prospectively studied interrupted versus continuous imatinib in patients with advanced GIST, 25 patients were identified with nonmetastatic primary GIST. Fifteen (60%) had a partial response and 9 (36%) went on to resection. Of those 9 patients, median treatment duration was 7.3 months, and 7 had an R0 resection,²⁰ which is comparable to the rate reported by Eisenberg et al.¹⁵

Although the studies discussed earlier had patients take imatinib up to the day before surgery, the authors of this case report allowed their patient to discontinue imatinib 3 weeks earlier to maximize her surgical stamina. In fact, she was hospitalized twice while on neoadjuvant imatinib. The first admission occurred days after initiation of treatment for nausea, vomiting, and fevers and was thought to be secondary to treatment-related tumor necrosis and likely translocation of intraluminal bacteria into the tumor. Her second admission was also infection-related, most likely a viral parotitis/pneumonitis. Pyrexia is reported commonly in clinical trials of imatinib for hematologic malignancies, although less so (13%) for GIST.²¹ Infection of any grade is described in 15.5% of patients taking 400 mg of imatinib in the metastatic trials. Parotitis does not appear to have been reported, and interstitial pneumonitis is reported in fewer than 0.1% of cases. Opportunistic infections have been reported in patients treated with imatinib, including viral infections such as varicella zoster, hepatitis B reactivation, and Epstein-Barr virus-related lymphoproliferative disorder; interference with T-cell immunity is a postulated mechanism.²²

Risk of progression of GIST after resection is strongly linked to tumor size, mitotic rate, and location,^{3,5} although these factors were largely validated before the adjuvant imatinib era. In the prospective neoadjuvant studies described earlier, 2-year progression-free survival was 83% to 87% and recurrence rate was 30% to 32% at a median follow-up of 3 years. Based on pretreatment tumor size (>10 cm), the authors plan to give 36 months of adjuvant imatinib, as recommended in the GIST section of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Soft Tissue Sarcoma (footnote c on page GIST-1, available online at NCCN.org).²³

Conclusions

No high-level evidence exists supporting the routine use of imatinib in the neoadjuvant setting for GIST. The NCCN Guidelines²³ recommend treating patients on an individual basis (category 2A; available at NCCN.org). Currently, borderline resectable tumors (ie, those threatening or encroaching on adjacent organs) or recurrent oligometastatic tumors are reasonable candidates for this approach. Tumor size, mitotic rate, and location may all play a role in stratifying which patients may benefit most.

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Post-Test Questions

1. True or False: The optimal duration of neoadjuvant therapy in GIST is currently unknown.
2. Factors predictive of tumor recurrence after resection include:
 - a. Size
 - b. Mitotic rate
 - c. Location of the primary tumor
 - d. All of the above
3. True or False: Currently, imatinib 400 mg daily is recommended as the standard dose, with dose escalation up to 800 mg for treatment failure.