Pathologic Complete Response in a Large Gastric GIST: Using Molecular Markers to Achieve Maximal Response to Neoadjuvant Imatinib

Joshua B. Brown, MD, MSc^a; Reetesh K. Pai, MD^b; Melissa A. Burgess, MD^c; Jennifer Chennat, MD^d; and Amer H. Zureikat, MD^a

Abstract

Gastrointestinal stromal tumors (GISTs) represent 1% of alimentary tract neoplasms. Up to 90% of GISTs are driven by activating mutations in tyrosine kinase *KIT* or *PDGFRα* genes. Imatinib mesylate is a tyrosine kinase inhibitor that has recently been used in a neoadjuvant role for locally advanced GIST. Pathologic complete response (pCR) to imatinib, however, is rare and may be limited to patients with certain mutations. We report on a 71-year-old woman with a large advanced gastric GIST near the gastroesophageal junction initially involving the pancreas, spleen, adrenal, and aortic wall. The tumor harbored a *KIT* exon 11 deletion mutation in codon 558, which predicts a favorable response to imatinib. After 6 months of neoadjuvant imatinib therapy, the tumor was downstaged to allow partial gastric resection without the need for total gastrectomy reconstruction. The patient underwent partial gastrectomy, distal pancreatectomy, and splenectomy, and histologic examination showed a margin-negative resection with a near-pCR, with <5% viable tumor. Prolonged neoadjuvant therapy was undertaken based on the prognostic significance of a *KIT* exon 11 deletion mutation in codon 558, which facilitated an R0 resection while minimizing the surgical extent of the resection. A near-pCR of a large gastric GIST after neoadjuvant imatinib therapy remains a rare occurrence. Molecular testing should be undertaken before neoadjuvant therapy, because specific mutations can identify patients who will respond to imatinib and those likely to achieve significant downstaging and pCR.

J Natl Compr Canc Netw 2018;16(12):1424–1428
doi: 10.6004/jnccn.2018.7063

Gastrointestinal stromal tumors (GISTs) are a class of subepithelial mesenchymal neoplasms typically arising in the alimentary tract from the interstitial cells of Cajal, and represent 1% of primary gastrointestinal tract cancers. Up to 90% of GISTs are driven by an activating mutation in the *KIT* or *PDGFRα* genes, which encode tyrosine kinase proteins.¹ *KIT* mutations are most common, and molecular analysis has identified a number of mutation locations, including exons 9, 11, 13, and 17. Imatinib mesylate, a tyrosine kinase inhibitor, has shown efficacy in advanced and metastatic GIST.² More recently, imatinib has been used in the neoadjuvant setting in an effort to downstage tumors, with studies

showing its ability to reduce the morbidity associated with surgical resection and facilitate an R0 resection in up to 91% of patients.^{3,4}

Despite this success, pathologic complete response (pCR) to neoadjuvant imatinib remains rare, and the indications and duration of therapy are less well-defined.⁵ Recent data suggest that specific mutations giving rise to GIST appear to have prognostic significance, primarily through responsiveness to imatinib therapy, with *KIT* exon 11 mutations showing a superior response.⁶ This report describes a patient with locally advanced gastric GIST harboring a *KIT* exon 11 mutation who experienced a near-pCR to neoadjuvant imatinib.

^aDivision of Surgical Oncology, ^bDepartment of Surgical Pathology, ^cDepartment of Medical Oncology, and ^dDivision of Gastroenterology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania. Submitted May 10, 2018; accepted for publication July 23, 2018. The authors have disclosed that they have no financial interests,

arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Amer H. Zureikat, MD, Division of Surgical Oncology, University of Pittsburgh Medical Center, 5150 Centre Avenue, Suite 421, Pittsburgh, PA 15232. Email: zureikatah@upmc.edu

Case Presentation

A 71-year-old woman with a medical history of chronic obstructive pulmonary disease on 3 liters of home oxygen presented to her local hospital with a 2-day history of melena and dizziness. She was noted to have anemia, with a hemoglobin level of 7.9 g/dL. She was initially treated with proton pump inhibitors, received 2 units of packed RBCs, and underwent upper and lower endoscopy. Upper endoscopy revealed erosive gastritis and a submucosal mass. She was referred to the University of Pittsburgh Medical Center for an endoscopic ultrasound, which revealed an 8.7-cm gastric cardia tumor. Biopsy results revealed spindle cell–type GIST with immunohistochemistry staining positive for C-kit and DOG-1, and negative for desmin and S-100. CT of the chest, abdomen, and pelvis revealed an 11.3 x 9.8-cm lobular mass arising from the posterior stomach abutting the superior pole of the spleen, distal pancreas, adrenal gland, and lateral aortic wall with features of central necrosis (Figure 1). No suspicious adenopathy or evidence of metastasis was present. The absence of metastasis was confirmed with PET/CT (Figure 2). Molecular analysis of the biopsy tissue revealed a *KIT* exon 11 p.E544_K558del mutation.

After multidisciplinary discussion, the patient was started on 400 mg/d of oral imatinib with plans for 4 to 6 months of neoadjuvant therapy to maximize tumor response in the presence of a *KIT* exon 11 K588 deletion mutation. CT of the abdomen and pelvis at 2 months after imatinib initiation showed a treatment response, with an interval decrease in tumor size to 7.8 x 6.0 cm and a decrease in tumor den-

sity. Imaging at 4 months showed continued interval decrease in tumor size. At 6 months after initiation of imatinib, the tumor no longer abutted the adrenal gland or lateral aortic wall, and measured 7.5 x 5.7 cm in maximal diameter (Figure 3). The patient had tolerated neoadjuvant therapy well, with minor side effects including anemia requiring blood transfusion, myalgias, facial rash, anorexia, and mild elevation of lactate dehydrogenase level, with no serious adverse events. Given the good response to neoadjuvant therapy, she was offered surgical resection. Imatinib was stopped for 3 weeks preoperatively.

Exploratory laparotomy showed that the mass involved the gastric cardia, distal pancreas, and splenic hilum. After dissection and mobilization of the stomach and intra-abdominal esophagus, it became apparent that the mass could be resected by partial (wedge) gastrectomy without need for reconstruction. Furthermore, the tumor did not involve the aorta or left adrenal gland. A partial gastrectomy was performed with en bloc distal pancreatectomy and splenectomy. Her postoperative course was uneventful; an upper gastrointestinal series obtained on postoperative day 4 showed no leak from the gastric resection line. She was discharged home on postoperative day 7, and will continue imatinib, 400 mg orally for at least 3 years.

Pathologic examination of the resected specimen revealed a 6.8-cm predominantly nonviable GIST with metaplastic ossification (Figure 4). All surgical margins were negative. The mitotic index was 0 mitoses per 5 mm². Only focal areas of viability were demonstrated by positive immunohistochemistry staining of C-kit, DOG-1, and CD34 in <5% of

Figure 1. Preneoadjuvant treatment CT scan showing large, locally advanced gastric gastrointestinal stromal tumor.

Figure 2. PET/CT of the locally advanced gastric gastrointestinal stromal tumor.

Figure 3. Postneoadjuvant treatment CT scan showing response of locally advanced gastric gastrointestinal stromal tumor to imatinib treatment.

the tumor. No angiolymphatic invasion was seen and 0 of 7 lymph nodes were negative, yielding a pathologic tumor stage of ypT2N0 with near-pCR to neoadjuvant imatinib.

Discussion

A pCR is a rare occurrence for a large gastric GIST. Our report presents a near-pCR of a gastric GIST harboring a *KIT* exon 11 K588 deletion mutation after prolonged treatment with imatinib. Based on the molecular profile of the tumor, prolonged neoadjuvant therapy was undertaken to achieve 2 specific objectives. First, given the patient's comorbidities, we aimed to sufficiently downstage the tumor to avoid a total gastrectomy, particularly because initial imaging showed the tumor in proximity to the gas-

troesophageal junction, likely requiring a total gastrectomy. Second, initial imaging also showed abutment of the aortic wall, increasing the likelihood of a margin-positive resection with upfront surgery. Prolonged neoadjuvant therapy sufficiently shrank the tumor off the aorta and facilitated an R0 resection. Despite the large tumor size, identification of a *KIT* exon 11 deletion mutation including codon 558 predicted a favorable response to imatinib, enabling a margin-negative resection with a potentially less morbid operation.

Since the first report of GIST response to imatinib, this agent has revolutionized the therapeutic approach to this disease, which previously had no effective therapies.⁷ Despite this, pCR after neoadjuvant imatinib remains rare (Table 1). The first report was in 2003 by Scaife et al⁸ of 2 patients with pCR from 126 patients treated with imatinib for unresectable GIST. Since then, pCR has been reported in case reports or small series ranging from 1% to 16% of resected tumors.^{9–18} Many of the reported pCRs, however, occurred in patients with colorectal or pelvic GIST.^{11,12,18}

Molecular features have a significant impact on prognosis in GISTs, particularly with regard to imatinib response.¹ Mutations in the *KIT* gene are the most common, accounting for 80% to 85% of GIST mutations, with *PDGFRα* mutations representing 5% to 10% of mutations. The remaining mutations have been termed *wild-type*; however, *SDH* and *BRAF* mutations have been identified among these tumors. Within the *KIT* gene, exon 11 mutations are most common, accounting for 70% of cases, whereas exon 9 mutations account for 10% to 15%. Patients

Figure 4. (A) Gross examination of the resection specimen demonstrated a 6.8-cm lobulated mass involving the wall of the stomach and abutting the spleen and pancreas. (B) Histologic examination showed nonviable tumor composed predominantly of collagen without tumor cells (hematoxylin-eosin, original magnification x40). (C) Focal areas of viable tumor cells with a spindled morphology and accounting for <5% of the overall tumor were identified (hematoxylin-eosin, original magnification x100).

Pathologic Complete Response in Gastric GIST

Table 1. Reports of Pathologic Complete Response in Advanced Gastrointestinal Stromal Tumors

Reference	N	Duration of Neoadjuvant Imatinib (mo) ^a	Mutation Identified
Rutkowski et al ⁴	3	NR	NR
Scaife et al ⁸	2	10	NR
Andtbacka et al ⁹	3	NR	NR
Bonvalot et al ¹⁰	2	NR	NR
Cheng et al ¹¹	12	11	<i>KIT</i> exon 11 (all 12 patients)
de Azevedo et al ¹²	1	18	NR
Goh et al ¹³	3	6	NR
Melichar et al ¹⁴	1	6	<i>KIT</i> exon 11 W557_V559delinsF
Quezada et al ¹⁵	1	10	NR
Rediti et al ¹⁶	1	NR	NR
Suzuki et al ¹⁷	1	35	NR
Salazar et al ²⁰	1	12	<i>KIT</i> exon 11 6bp deletion
Chacon et al ²⁴	1	13	NR

Abbreviation: NR, not reported.

^aMedian number of months for series with >1 patient.

with exon 9 mutations should be considered for imatinib dose escalation to 800 mg daily. These mutations may be less responsive to imatinib, and higher dosing regimens have been associated with improved progression-free survival in advanced GIST.⁶ Exon 13, 14, and 17 mutations have also been identified, representing 1% to 2% of cases, respectively.

Further differences in prognosis and response have been identified based on the type of *KIT* exon 11 mutation. Deletion mutations exhibit aggressive behavior compared with other types of mutations, particularly deletions in the 557/558 codons, as seen in our patient.¹⁹ Analysis of the ACOSOG Z9001 trial showed improved recurrence-free survival among patients receiving imatinib with *KIT* exon 11 deletions compared with those with point mutations or insertions of exon 11 at a median follow-up of 74 months.⁶ To our knowledge, all reported mutations among patients with pCR after neoadjuvant imatinib involve *KIT* exon 11 mutations, including our case.^{11,14,20} Of the specific mutations identified in prior reports, each was a deletion.^{14,20} Thus, molecular analysis may prove useful in delineating the potential for pCR and clinical response to imatinib.

A neoadjuvant approach to locally advanced GIST is being increasingly used; however, the indica-

tions and optimal duration of neoadjuvant imatinib are not well-defined. In this case report, a prolonged neoadjuvant strategy was successful in minimizing surgical morbidity while maximizing the potential for an R0 resection. Early phase II trials used neoadjuvant therapy for 2 to 3 months, and reported R0 resection rates of 67% to 77%^{21,22}; however, a more recent phase II trial treated patients for 6 to 9 months and reported an R0 resection rate of 91%.³

Several retrospective series have also reported on outcomes after longer neoadjuvant therapy with imatinib,^{4,9} with evidence suggesting that the optimal response may be between 7 to 12 months.^{4,9,23} Neoadjuvant imatinib duration in patients with a reported pCR (including the current report) was a mean of 11.3 months, with a range of 6 to 35 months.^{8,11–15,17,20,24} However, in some reports it is unclear whether imatinib served as true neoadjuvant therapy (with the intent for resection made upfront at treatment initiation) or as definitive therapy in patients with unresectable disease who eventually underwent resection after significant downstaging.⁸ Current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for GIST recommend neoadjuvant therapy be considered if it could reduce surgical morbidity through downstaging the tumor.²⁵ NCCN Guidelines note that therapy may require treatment for 6 months to achieve maximal response, and recommend mutation testing to ensure a favorable genotype for imatinib response. Given the promising results of small series and phase II trials, larger trials are warranted to further elucidate the optimal neoadjuvant regimen for advanced GIST.

Conclusions

We report the near-pCR of a large gastric GIST after neoadjuvant imatinib therapy. This remains a rare occurrence after GIST resection and was facilitated by prolonged imatinib therapy in the presence of a *KIT* exon 11 K558 mutation. This case report highlights the importance of molecular testing before neoadjuvant imatinib for GIST, because certain mutations can identify patients more likely to benefit from significant tumor downstaging and pathologic response.

References

1. Oppelt PJ, Hirbe AC, Van Tine BA. Gastrointestinal stromal tumors (GISTs): point mutations matter in management, a review. *J Gastrointest Oncol* 2017;8:466–473.
2. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;347:472–480.
3. Kurokawa Y, Yang HK, Cho H, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. *Br J Cancer* 2017;117:25–32.
4. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. *Ann Surg Oncol* 2013;20:2937–2943.
5. Koontz MZ, Visser BM, Kunz PL. Neoadjuvant imatinib for borderline resectable GIST. *J Natl Compr Canc Netw* 2012;10:1477–1482; quiz 1482.
6. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol* 2014;32:1563–1570.
7. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001;344:1052–1056.
8. Scaife CL, Hunt KK, Patel SR, et al. Is there a role for surgery in patients with “unresectable” cKIT+ gastrointestinal stromal tumors treated with imatinib mesylate? *Am J Surg* 2003;186:665–669.
9. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol* 2007;14:14–24.
10. Bonvalot S, Eldweny H, Pechoux CL, et al. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol* 2006;13:1596–1603.
11. Cheng CT, Tsai CY, Yeh CN, et al. Clinical significance of pathological complete response in patients with metastatic gastrointestinal stromal tumors after imatinib mesylate treatment—lessons learned. *Anticancer Res* 2014;34:6617–6625.
12. de Azevedo CR, Paiva TF Jr, Rossi BM, et al. Pathologic complete response with neoadjuvant imatinib for locally advanced pelvic GIST. *Int J Clin Oncol* 2011;16:279–283.
13. Goh BK, Chow PK, Chuah KL, et al. Pathologic, radiologic and PET scan response of gastrointestinal stromal tumors after neoadjuvant treatment with imatinib mesylate. *Eur J Surg Oncol* 2006;32:961–963.
14. Melichar B, Voboril Z, Nozicka J, et al. Pathological complete response in advanced gastrointestinal stromal tumor after imatinib therapy. *Intern Med* 2005;44:1163–1168.
15. Quezada N, Acevedo F, Maramba A, et al. Complete pathological response to imatinib mesylate in an extraintestinal gastrointestinal stromal tumor. *Int J Surg Case Rep* 2014;5:681–685.
16. Rediti M, Pellegrini E, Molinara E, et al. Complete pathological response in advanced extra-gastrointestinal stromal tumor after imatinib mesylate therapy: a case report. *Anticancer Res* 2014;34:905–907.
17. Suzuki S, Sasajima K, Miyamoto M, et al. Pathologic complete response confirmed by surgical resection for liver metastases of gastrointestinal stromal tumor after treatment with imatinib mesylate. *World J Gastroenterol* 2008;14:3763–3767.
18. Machlenkin S, Pinski I, Tulchinsky H, et al. The effect of neoadjuvant Imatinib therapy on outcome and survival after rectal gastrointestinal stromal tumour. *Colorectal Dis* 2011;13:1110–1115.
19. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer* 2008;112:608–615.
20. Salazar M, Barata A, André S, et al. First report of a complete pathological response of a pelvic GIST treated with imatinib as neoadjuvant therapy. *Gut* 2006;55:585–586.
21. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol* 2009;99:42–47.
22. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. *Ann Surg Oncol* 2012;19:1074–1080.
23. Tirumani SH, Shinagare AB, Jagannathan JP, et al. Radiologic assessment of earliest, best, and plateau response of gastrointestinal stromal tumors to neoadjuvant imatinib prior to successful surgical resection. *Eur J Surg Oncol* 2014;40:420–428.
24. Chacon M, Roca E, Huertas E, et al. CASE 3. Pathologic complete remission of metastatic gastrointestinal stromal tumor after imatinib mesylate. *J Clin Oncol* 2005;23:1580–1582.
25. von Mehren M, Randall RL, Benjamin RS, et al. NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma. Version 2.2018. To view the most recent version of these guidelines, visit NCCN.org. Accessed April 25, 2018.