

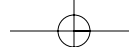


CASE STUDY

M O N O G R A P H

Case Studies
in the
Management
of Advanced
GIST With
Imatinib

 **NOVARTIS**
ONCOLOGY



Case Studies in the Management of Advanced GIST With Imatinib

CASE STUDY MONOGRAPH

Guest Editor:

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PREFACE

Case Studies in the Management of Advanced Gastrointestinal Stromal Tumor With Imatinib

The description of gastrointestinal stromal tumor (GIST) as a distinct disease entity has emerged only during the past 15 years. In 2002 imatinib was approved for adult patients with KIT (CD117)-positive unresectable and/or metastatic malignant GIST, for which no prior therapy has proved effective. Since then, imatinib has become the standard of care. In 2004 both the European Society of Medical Oncology and the National Comprehensive Cancer Network held multidisciplinary consensus meetings to develop guidelines for the management of GIST.^{1,2} The guidelines emphasize the increasing understanding that optimal management of GIST involves a multidisciplinary team incorporating pathology, surgical oncology, medical oncology, and imaging experts throughout the process, including initial evaluation, management, and follow-up.

Through case histories, this monograph offers insight into how experts approach the use of imatinib in the treatment of advanced GIST. The introduction, by Heikki Joensuu, MD, reviews current management of metastatic or unresectable GIST. The cases presented by international experts illustrate a range of clinical challenges, including metastatic GIST that is completely resectable at presentation, objective response to imatinib, stable disease with imatinib, secondary progression on imatinib, imatinib treatment interruptions, and inconsistent response to imatinib.

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INTRODUCTION: CURRENT MANAGEMENT OF METASTATIC OR UNRESECTABLE GIST

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Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm (sarcoma) of the gastrointestinal tract, accounting for 70% to 90% of those tumors.³⁻⁵ In Caucasian populations, the annual incidence is 10 to 15 cases per million.^{6,7}

Gastrointestinal stromal tumors may arise anywhere along the gastrointestinal tract, but most originate from either the stomach or the small intestine.⁸ GISTs usually express the KIT protein, a receptor tyrosine kinase encoded by the *KIT* gene located in chromosome 4q12. The ligand for KIT is stem-cell factor.

Although approximately 80% of GISTs harbor mutated *KIT*, 1% to 5% have mutated *PDGFRA*.⁹⁻¹¹ Mutations of these 2 receptor tyrosine kinase genes are considered important initiating events in the molecular pathogenesis of most GISTs. In untreated GISTs, *KIT* mutations are limited to certain exons of the gene: approximately 65% of GISTs have a mutation in *KIT* exon 11, which encodes the intracellular juxtamembrane domain of the KIT protein; 15% to 20% are found in exon 9, which encodes the proximal extracellular part of the protein; and only approximately 2% of GISTs have mutations in exon 13 or 17, which encode parts of the intracellular kinase domain.⁹⁻¹¹

Gastrointestinal stromal tumors vary greatly in their malignant potential. Small, slowly proliferating GISTs seldom give rise to metastases, whereas large tumors (>5 to 10 cm in diameter) with many mitoses (>5 mitoses per 50 high-power fields [HPF]) frequently give rise to liver metastases and intra-abdominal implants.² Size and mitotic count are thus important factors in defining high-risk GIST (**Table 1**).¹²

Surgery is the standard treatment for primary localized GIST. In the US National Cancer Institute

Table 1. Definition of High-Risk GIST

| Size | Mitotic Count |
|----------|------------------|
| >5 cm | >5/50 HPF |
| >10 cm | Any mitotic rate |
| Any size | >10/50 HPF |

HPF, high-power fields.

Adapted with permission from Fletcher CDM, Berman JJ, Gorstein F, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002;33:459-465.¹²

(NCI) Surveillance, Epidemiology, and End Results registry data of patients diagnosed with GIST from 1992 to 2000, the relative 5-year survival was 45%.⁸ In the past, patients with GIST with distant metastases had a bleak outcome, with median survival ranging from 10 to 20 months.¹³ Outcomes for patients diagnosed with advanced GIST improved markedly when imatinib, a selective inhibitor of KIT and platelet-derived growth factor receptor (PDGFR), was found to be effective in the treatment of GIST.¹⁴⁻¹⁶

Management of Metastatic and Inoperable GIST

Response to imatinib therapy

In the US-Finland Study (B2222), the median duration of response to imatinib was 27 months at a median follow-up of 64 months (data on file, Novartis Pharmaceuticals),^{17,18} and some patients have responded for 5 years or longer. Approximately 84% of patients experienced tumor control with imatinib (objective tumor response, 68%; stable disease, 16%). Two patients achieved a sustained, complete tumor response. The median onset of response was 13 weeks; however, response occurred more than 6 months after treatment initiation for more than 25% of responding patients. Based on the Southwest Oncology Group criteria, patients with stable disease achieved similar survival to those with a partial response, suggesting that lesion volume reduction in response to imatinib therapy may not be an important prognostic factor. At a median follow-up of 64 months, the median overall survival was 58 months (data on file, Novartis

Pharmaceuticals).^{17,18} These findings suggest that imatinib treatment may prolong survival up to 4-fold compared with historical controls.¹⁹ Following initiation of imatinib therapy, responding liver metastases characteristically become hypodense on computed tomography (CT) or magnetic resonance imaging (MRI), resulting from GIST cell apoptosis leading to hyaline degeneration of cellular tumor tissue.¹⁴ Hypodense GIST metastases are better delineated and more easily detected by CT scan than the denser, untreated GIST lesions.²⁰ Consequently, the appearance of new, small, hypodense liver lesions on CT scan following imatinib therapy should not be misinterpreted as tumor progression. In problematic cases, ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography (¹⁸FDG-PET) may aid in differentiating response from progression. Decreased density of metastatic lesions usually signals response and reduced lesion volume.

Imatinib dosing

The standard starting dose of imatinib is 400 mg/d. In 2 clinical studies (Study B2222 and an intergroup study S0033), the daily dose of imatinib was escalated to 800 mg in patients progressing at the lower daily doses of 400 mg or 600 mg.²¹ The daily dose was escalated to 800 mg in a total of 103 patients; 6 patients achieved a partial response and 21 maintained stable disease after dose escalation, for an overall clinical benefit of 26%. From the safety data available, escalating the dose to 800 mg daily in patients progressing at lower doses of 400 mg or 600 mg daily does not seem to affect the safety profile of imatinib.

Imatinib treatment duration

It is recommended that imatinib be administered continuously.^{1,22} In clinical trials, treatment was continued until disease progression.²¹

Management of adverse events

Because imatinib dose reductions are best avoided, it is important to know how to manage common adverse events. The majority of patients treated with imatinib experience adverse events at some time. Many are mild to moderate in severity and tend to decrease over time, and thus may not require any specific therapy.¹⁶ The most frequent adverse events ($\geq 10\%$ of patients) associated with imatinib are periorbital or leg edema, occasional

muscle cramps, diarrhea, nausea/vomiting, fatigue, abdominal pain, muscle pain, and skin rash. Grade 1/2 thrombocytopenia, anemia, and neutropenia are also frequent. Elevation of serum transaminase levels occurs in $>1.0\%$ but $\leq 10\%$ of patients. Certain adverse events are easily managed: periorbital edema often responds to diuretics, and nausea may be alleviated when the daily imatinib dose is divided and administered twice a day (BID). Imatinib therapy requires close surveillance especially in the beginning of therapy, when the patient is elderly or frail, or when multiple concomitant medications are used. Generalized skin rash or edema, grade 3 or 4 cytopenias (except anemia), and dyspnea require prompt interruption of imatinib administration and may require subsequent dose reduction.²¹ Reinstitution of therapy is the goal after treatment interruption for adverse events.

Surveillance

Response to imatinib is usually monitored with CT or sometimes with MRI. Baseline imaging is best done within 2 weeks before initiation of imatinib, as some GISTs grow rapidly. No study has evaluated the frequency of follow-up examinations, and the optimal frequency of imaging examinations is unknown. The first follow-up CT is often carried out 1 to 2 months after the first imatinib administration, and the subsequent evaluations then take place at approximately 3-month intervals. Metabolic imaging with ¹⁸FDG-PET may help in clinical decision making.²²

Emerging Approach to Surgery in the Management of Metastatic GIST

Excision of all macroscopic disease following response to imatinib may reduce the risk of emergence of imatinib-resistant tumor clones. Some patients who have had all macroscopic disease removed by surgery and who have continued imatinib therapy have had durable responses.^{23,24} The best timing for such surgery is while the tumors are responding to imatinib. At the present time, this strategy is experimental, as no randomized study has yet addressed the benefits and risks of metastasectomy in patients who respond to imatinib.²³ Patients with bleeding, infected, or obstructive metastases may benefit from palliative surgery.

Treatment of Imatinib-Resistant GIST

Most GISTs eventually cease to respond to imatinib because they develop secondary resistance. Secondary resistance is often defined as resistance occurring beyond the first 6 months of imatinib therapy.^{1,8} It can be either multifocal or partial (one or a limited number of metastases showing a nodule within a mass and/or enlargement with increased FDG uptake on PET scan, while other sites remain controlled by imatinib). GISTs may harbor secondary *KIT* mutations that were not present or were not detectable before initiation of imatinib treatment. Interestingly, secondary mutations often occur at regions of the *KIT* gene that encode parts of the KIT protein that affect imatinib binding, such as the adenosine triphosphate/imatinib binding pocket (encoded by exons 13 and 14) or the activation loop (exon 17) of the KIT kinase.²⁵ Other resistance mechanisms likely exist.

Recurrent disease can take the form of a new lesion at the site of surgical resection, an increase in size of an existing lesion, a new metastasis, or development of an intratumoral nodule (“node within a lesion” or “nodule within a mass”).¹ Resistant liver lesions often emerge within or at the border of a responding (hypodense) metastasis and can be seen as a node within a lesion upon imaging. Such nodules frequently harbor a secondary *KIT* mutation.²⁶ When other metastatic lesions continue to respond, consider surgical resection of a growing single lesion (or a few such lesions). Radiofrequency ablation may be attempted when surgery is not feasible.

Compliance with imatinib administration should be assessed when GIST progresses during therapy. Imatinib dose escalation up to 800 mg/d is recommended whenever feasible in patients who progress on a lower dose of imatinib. Approximately 5% of patients who progress on the standard dose of imatinib achieve a partial response after dose escalation, and another 30% develop stabilization of the disease.^{27,28} Patients who have disease progression and who continue to progress

Table 2. Key Principles in the Management of Metastatic or Inoperable GIST

| Clinical Scenario | Management |
|--|--|
| <p>First-line therapy</p> <p>Systemic therapy</p> <p>Surgery</p> | <ul style="list-style-type: none"> • Imatinib daily until treatment failure; the starting dose is usually 400 mg/d • Monitor blood cell counts, blood chemistry, and treatment response (eg, CT of the abdomen 1 month after starting imatinib, then at about 3-month intervals) • Surgical resection of residual tumors of responding patients may be considered in selected cases, but the benefit is unproven • Removal of bleeding, infected, or obstructing metastases may be necessary |
| <p>GIST progresses during imatinib therapy</p> | <ul style="list-style-type: none"> • Consider surgery for solitary growing metastases <ul style="list-style-type: none"> – Assess compliance with imatinib administration – Escalate imatinib dose up to 800 mg/d if feasible – Check pharmacokinetics and comedication (patients who take enzyme-inducing antiepileptic drugs may need a higher-than-standard imatinib dose) • Consider sunitinib malate as second-line systemic therapy or participation in a clinical trial with novel agents |

despite imatinib dose escalation are candidates for a trial with other tyrosine kinase inhibitors.²² Sunitinib malate has been approved for the treatment of patients with GIST whose disease has progressed or who are unable to tolerate treatment with imatinib. The principles of the management of advanced GIST are summarized in **Table 2**. ■

CASE STUDIES

ADVANCED GIST



METASTATIC GIST COMPLETELY RESECTABLE AT PRESENTATION

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This case study illustrates a situation in which resection of liver metastases was inappropriate because of the short time between resection of the primary tumor and development of the metastases. The treatment of choice was imatinib therapy. Attenuation of the original lesions on CT scan 7 months after initiation of imatinib therapy indicated response to imatinib; decreased tumor density during imatinib therapy is another indicator of treatment response. The hypodense lesion, visible because of apoptosis of a previously isodense metastasis, did not indicate progression. Thus, continued administration of imatinib was the appropriate treatment decision.

Case Presentation

Case history: At 1 year after resection of a GIST of the small intestine, a 67-year-old patient developed 2 liver metastases, detectable on an unenhanced CT scan (**Figure 1**). A thoracic CT was normal.

Figure 1. Unenhanced Image of the Liver

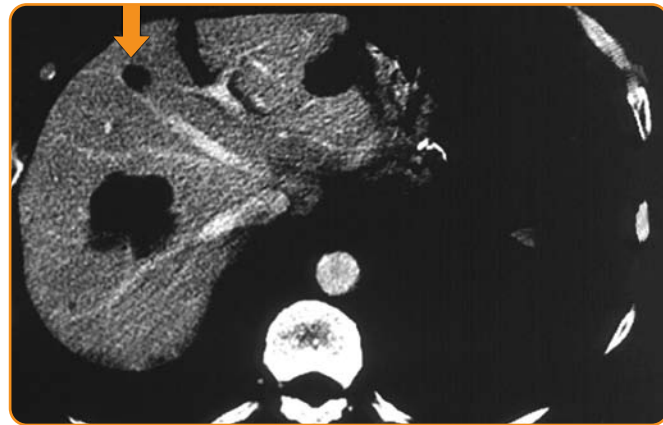


Two liver metastases were detectable on an unenhanced image in August 2001. Figure provided courtesy of Sylvie Bonvalot, MD, PhD.

Imatinib therapy: Although surgery was theoretically possible, it was not appropriate for this patient because of the short time between the occurrence of the primary lesion and the metastases. Imatinib, which is indicated for first-line treatment of metastatic GIST, was the treatment of choice.

At 7 months after treatment initiation, a portal venous phase image on CT revealed a new hypodense lesion (**Figure 2**). The original lesions had darkened, indicating response to imatinib. Imatinib therapy was continued.

Figure 2. A Portal Venous Phase Image on CT Taken in March 2002



Darkening of lesions indicates response to imatinib after 7 months of imatinib therapy. Figure provided courtesy of Sylvie Bonvalot, MD, PhD.

Localized progression: After 33 months of imatinib treatment, the patient developed a localized progression (**Figure 3**). The progression was treated by percutaneous radiofrequency. Imatinib therapy was maintained at 400 mg/d.

Figure 3. CT Scan Showing Progression



After 33 months of imatinib therapy, localized progression was observed on CT scan. Figure provided courtesy of Sylvie Bonvalot, MD, PhD.

Metastasis: After 40 months of imatinib therapy, the patient developed global liver and peritoneal progression. At this point, the imatinib dose was increased to 800 mg/d.²⁸

Outcome: The patient has been switched to targeted therapy with sunitinib.

Discussion

Although surgery would have been possible for the 2 liver metastases, it was deemed to be inappropriate for this patient for 2 reasons: (1) the brief (1-year) interval between the occurrence of the primary tumor and the metastasis (patients whose liver metastases develop 2 or more years after resection of their primary tumor benefit most from surgical resection of liver metastases; some

patients survive more than 4 years after hepatic resection)²⁹; and (2) the demonstrated lack of or limited benefit of complete metastasectomy before initiation of imatinib versus therapy with imatinib alone.³⁰

The CT scans taken 7 months after treatment initiation revealed darkening of the original lesions, suggesting apoptosis of a previously isodense metastasis and indicating response to imatinib.²⁰ Thus, continued administration of imatinib is the appropriate treatment decision.

Progression-free survival following secondary surgery is similar to that reported among imatinib-treated patients who do not undergo surgery. The value of secondary resection should, therefore, be evaluated in randomized clinical trials.³¹ ■



METASTATIC GIST WITH OBJECTIVE RESPONSE TO IMATINIB

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This case illustrates the long natural history of some GISTs, with 16 years intervening between initial surgery and development of liver metastases. The primary tumor was diagnosed as leiomyosarcoma in the era before GIST was a well-recognized disease entity. This case also demonstrates the slow process of size reduction in some GIST metastases during imatinib therapy.

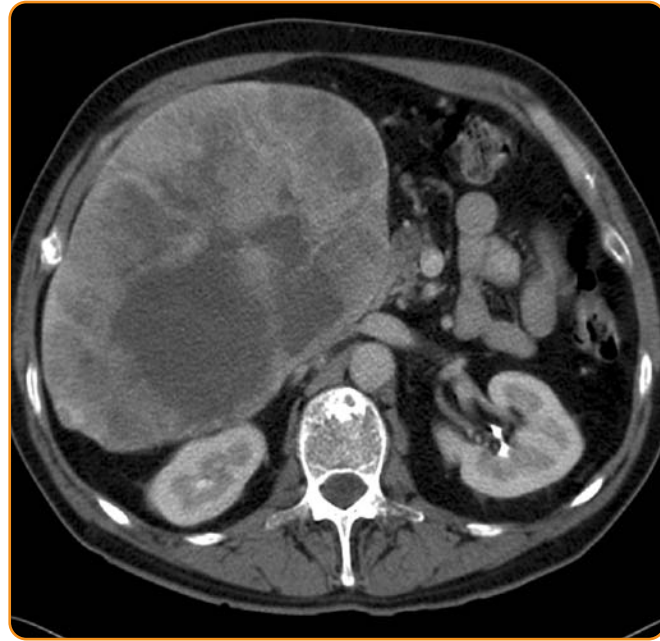
Case Presentation

Case history: A 36-year-old male experienced stomach pain and nausea in November 1984. In March 1985, an intra-abdominal tumor measuring approximately 10 cm in diameter was excised from the mesentery of the jejunum at laparotomy. No metastases appeared at laparotomy or in staging examinations. Based on histopathology, the tumor was diagnosed as leiomyosarcoma. No adjuvant chemotherapy or radiation therapy was administered following surgery. In 2000, the patient developed gradually worsening stomach pain and occasional emesis.

Diagnosis: Ultrasound examination of the abdomen in early 2001 revealed an upper abdominal tumor. A coarse needle biopsy revealed tissue morphology compatible with GIST. Immunostaining was strongly positive for KIT and faintly positive for smooth muscle actin; no desmin or CD34 expression was present. Five percent of the cells stained positive for the Ki-67 antigen on immunostaining. CT scanning identified 2 liver metastases: a large metastasis (20 × 13 cm) in segment V (**Figure 4**) and a smaller metastasis (2.8 cm in diameter) in segment IVA.

Imatinib therapy: Imatinib 400 mg/d was initiated in May 2001. By July 2003, both metastases had diminished in size. The larger metastasis was reduced

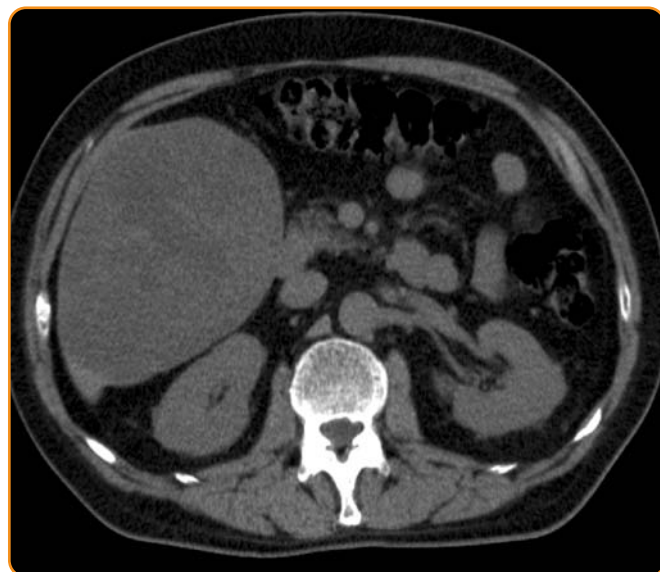
Figure 4. CT Scan Taken in Early 2001



A large liver metastasis appears anterior to the right kidney. Figure provided courtesy of Heikki Joensuu, MD.

to 14.2 cm in diameter (**Figure 5**) and the smaller one to 2.5 cm. The patient continued to complain of pain in the upper abdomen and in the right flank, especially when lying down.

Figure 5. CT Scan Taken in July 2003

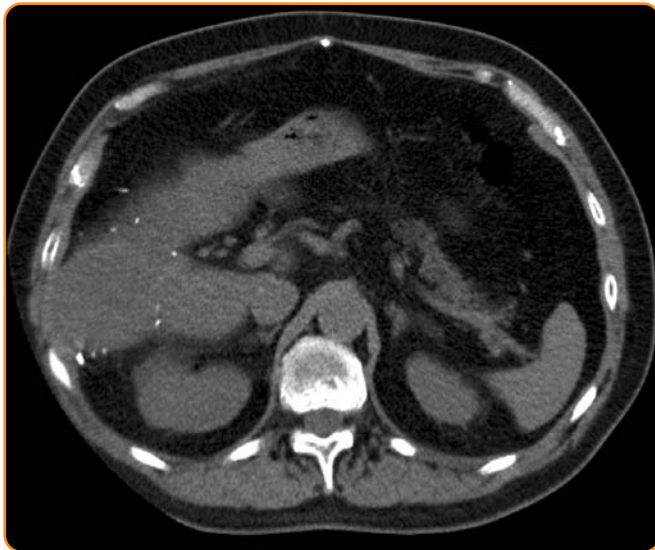


The bulky metastasis had decreased in size. Figure provided courtesy of Heikki Joensuu, MD.

Surgery: Both metastases were successfully resected in August 2003. Histopathologic examination of the excised tissue showed hyaline degeneration with few pycnotic (condensed and reduced in size) KIT-positive cells that did not stain with the MIB-1 proliferation marker. Postoperative CT scanning found no residual GIST.

Outcome: The patient's abdominal pain has been less troublesome since surgery. A follow-up CT scan, in September 2006, found no detectable metastases (**Figure 6**). As of this writing (March 2007), the patient is alive and continues to receive imatinib 400 mg/d.

Figure 6. Follow-up Scan Taken in September 2006



No residual disease is present at the resection site. Figure provided courtesy of Heikki Joensuu, MD.

Discussion

This case illustrates the long natural history of some GISTs. The primary tumor, diagnosed as leiomyosarcoma in the era before GIST was a well-recognized tumor entity, was removed in 1985. Liver metastases were not diagnosed until 2001, 16 years later. This case also demonstrates the slow process of size reduction in some GIST metastases during imatinib therapy.

Excision of the GIST metastases may have benefited the patient in 2 ways. First, his upper abdominal pain was likely related to the large liver metastasis. The pain was aggravated when the patient was

lying down, possibly because the tumor compressed the urinary tract or bowel, or caused stretching of tissues. Second, *KIT* mutations often affect the imatinib binding site and are an important mechanism for acquired resistance to imatinib.^{25,32} Removal of all macroscopic GIST tissue reduces the number of tumor cells, potentially lessening the risk for emergence of critical second mutations. The patient has been treated with imatinib for metastatic GIST for more than 5 years and currently has no evidence of disease.

No randomized trial has addressed the benefits and risks of debulking surgery in the treatment of advanced GIST. An exploratory analysis of the US-Finland Study (B2222) found that patients who had a small tumor burden at the time of initiation of imatinib therapy had a longer time to GIST progression than those with a large tumor burden.^{18,33} This finding might support debulking surgery and the adjuvant use of imatinib. This retrospective analysis may, however, have biases. Patients with a small tumor burden may have a less aggressive GIST than those who present with a large tumor mass, and patients with a small tumor mass may also have been diagnosed with metastatic disease at an earlier phase of the natural course of GIST.

Patients who respond to imatinib and who have been rendered free of all macroscopic disease have a longer time to disease progression than those who have undergone surgery for either limited or generalized GIST progression.^{23,24} Administration of imatinib following macroscopically complete resection of all metastatic disease is consistent with the labeling of imatinib for treatment of metastatic disease.

It is currently not known whether surgical removal of all detectable tumor tissue benefits patients who respond to imatinib and who have resectable disease. A prospective randomized trial is needed to address this question. The available data suggest that imatinib administration should be continued after surgical excision of all macroscopic disease, but it is not known whether it is necessary to continue imatinib administration for the rest of the patient's life in all cases. Selected patients who respond to imatinib and who have symptoms related to metastases may benefit from palliative excision of the metastases.²³ ■



METASTATIC GIST STABLE ON IMATINIB

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Stable disease is evidence of response to imatinib, but patients frequently expect tumor shrinkage, as illustrated by this case. Patient education is essential to dealing with this situation.

Case Presentation

Case history: An 81-year-old male patient was admitted in April 2006 for a GIST of the duodenum with initial metastatic spread to the peritoneum. The largest of the multiple metastatic masses was 8 cm. Multiple unmeasurable masses were also present.

Imatinib therapy: Imatinib was initiated at a dose of 400 mg/d. At the patient's first evaluation, after 2 months of therapy, his disease was stable. His tolerance of imatinib was acceptable, with limited periorbital edema. At 4- and 6-month follow-up visits, the patient's disease remained stable. He maintained that he was compliant to therapy, but he was discouraged by what he considered to be a lack of response to imatinib therapy. He requested that he be switched from imatinib treatment to a novel therapy.

Outcome: After a careful discussion with the patient, he understood the importance of maintaining imatinib treatment at the same dose and schedule.

Discussion

Patient education is essential to managing this situation. It was important to point out to the patient that tumor shrinkage is not the only evidence of response to imatinib. The 64-month data from the US/Finland (B2222) trial demonstrated that overall survival with imatinib is almost identical regardless of whether patients achieve stable disease or objective response (data on file, Novartis Pharmaceuticals).^{17,18} Furthermore,

some patients who initially had maintained stable disease as best response subsequently achieved partial response with longer treatment: 25% of patients responded after 6 months. If the patient had been experiencing imatinib treatment failure, however, either a new lesion with heterogeneous solid content or a nodule within a mass would have been visible on CT.¹

After explaining to the patient that the outcomes with stable disease and partial response are similar, maintenance of imatinib at an unchanged dose of 400 mg/d is appropriate management. Dose escalation of imatinib does not improve the response rate. In the US/Finland trial, the 400 mg/d dose was as effective as 600 mg/d.¹⁷

Switching to sunitinib in a patient with an imatinib-sensitive tumor who is not intolerant is hazardous and has never been explored in a clinical trial. ■



METASTATIC GIST WITH SECONDARY PROGRESSION ON IMATINIB: LIMITED FOCAL LESIONS

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Even patients with a good response to imatinib face the risk of developing new gene mutations resulting in progression of existing but “silent” tumor nodules. Surgery should always be considered if resistant foci can be completely resected, as in this case.

Case Presentation

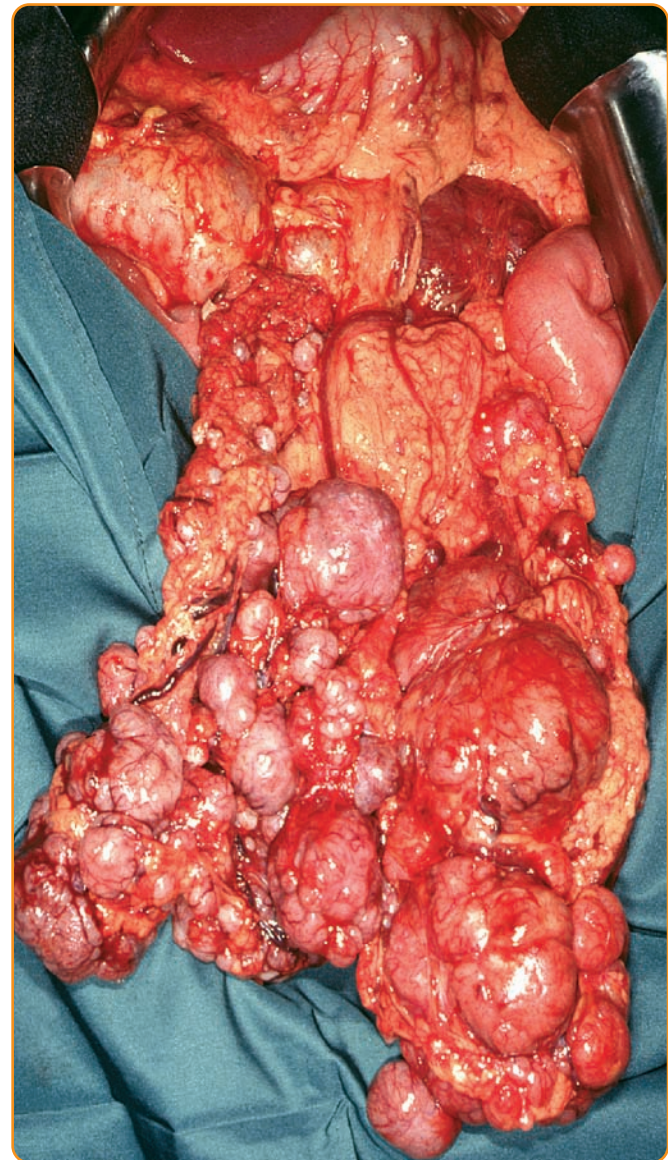
Case history: A 56-year-old man was admitted to the hospital in August 2000 with a history of 3 months of abdominal discomfort, occasional cramping pain, some abdominal distension, and general asthenia. His medical history was uneventful, except for hypertension controlled by diuretics and angiotensin-converting enzyme inhibitors.

Diagnosis: Abdominal ultrasound revealed limited ascites, as well as multiple nodules between the bowel segments, mainly in the lower abdomen. An abdominal CT scan confirmed these findings and revealed a mass at the ileocecal junction and extensive omental metastases. No liver metastases or lung nodules were detected, and there was no clinical evidence that extra-abdominal lymph node metastases were involved. An ultrasound-guided puncture showed a malignant mesenchymal tumor.

Surgery: At laparotomy, a peritoneal sarcomatosis was identified, with multiple nodes covering the omentum and the lower parts of the peritoneum (**Figure 7**). Frozen-section histology identified a spindle-cell tumor, which, in conjunction with the

ileocecal lesion, suggested a leiomyosarcoma. Because the primary tumor seemed to be located at the ileocecal valve, an ileocecal resection was performed. The procedure also included removal of the omentum and debulking of most abdominal nodules. Tumor reduction was estimated to be 80%. Based on the intraoperative pathology report of a malignant mesenchymal tumor, an intravenous port was inserted for postoperative chemotherapy. The patient recovered well from the operative procedure.

Figure 7. Initial Presentation of a Metastatic GIST of the Ileocecal Region Treated by Segmental Resection of the Ileum and Omentectomy in August 2000



Multiple nodules are present within the omentum and the peritoneal surface. Figure provided courtesy of Peter Hohenberger, MD.

Definitive histopathology identified a spindle-cell GIST within the 8-cm mass at the ileocecal valve. Mitotic count was very high: 90 mitoses per 50 HPF. Immunohistochemistry was positive for KIT (CD117) and PDGFR α ; weakly positive for CD34, actin, and vimentin; and negative for desmin and S100 protein. The MIB-1/Ki-67 index was 40%.

Phase 1 trial of imatinib: The patient was discharged in early September, with the option of systemic chemotherapy after 4 to 6 weeks to control the residual disease. When he presented again in October 2000, signs of recurrent peritoneal sarcomatosis were apparent (**Figure 8**). Meanwhile, *The New England Journal of Medicine* had published the first report on imatinib treatment for GIST.¹⁴ Consequently, the plan for systemic chemotherapy was abandoned, and the patient entered a phase 1 imatinib trial; he was treated with 400 mg BID.

Figure 8. Recurrent Peritoneal Sarcomatosis 3 Months After Removal of the Primary Tumor



Patient started treatment with imatinib 400 mg BID in December 2000. Figure provided courtesy of Peter Hohenberger, MD.

At his first evaluation, evidence suggested a partial remission, which was confirmed in March 2001. The patient's clinical condition consistently improved, and he remained free of tumor symptoms. Side effects of imatinib treatment were limited to periorbital pruritus and leg edema. He continued 800 mg/d of imatinib therapy, and tumor growth was well controlled over the next 2 years (**Figure 9**).

Figure 9. Response to Imatinib Showing a Complete Remission in March 2002



Molecular pathology had detected an 18-base-pair deletion in *KIT* exon 11. Figure provided courtesy of Peter Hohenberger, MD.

Two years after beginning treatment, the patient again developed abdominal pain and stool problems. Rectal enema showed a compression of the rectosigmoid junction, confirmed by abdominal CT scan. Because there were no signs of other GIST lesions in the abdomen, the decision was made to resect this unifocal mass (**Figure 10**). At laparotomy, several interenteric sarcomatous spots were removed, with no signs of a viable tumor or peritumoral angiogenesis. Pathology showed remnants of GIST with only apoptotic cellular figures and myxoid stroma. The 6-cm metastasis of viable GIST was removed by anterior resection.

Figure 10. CT Scan Taken 25 Months After Start of Imatinib

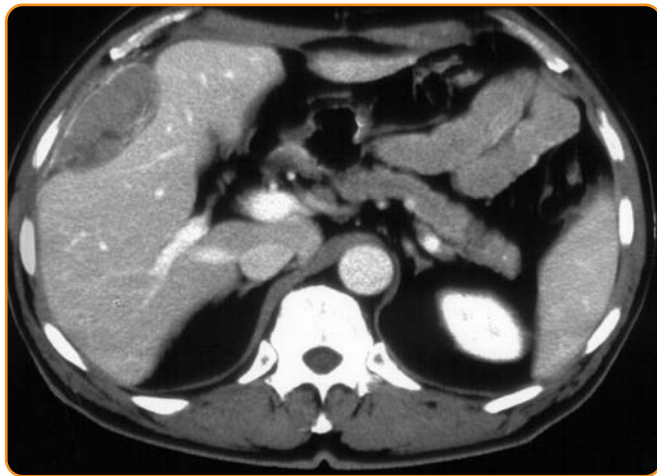


A peritoneal metastasis compressing the rectum is visible. The lesion was removed by anterior resection. Molecular pathology showed a *KIT* exon 17 mutation (D842V) not present in the initial tumor. Figure provided courtesy of Peter Hohenberger, MD.

Molecular pathology and exon analysis from the progressive metastasis at the rectum detected a mutation at *KIT* exon 17 (point mutation D842V) not present in the initial tumor. Mutational analysis of the primary tumor had identified an 18-base-pair deletion at *KIT* exon 11 (M552_W557del). (Mutational analysis performed and data provided by Eva Wardelmann, Department of Pathology, University of Bonn, Germany.)

The patient continued on imatinib 800 mg/d for continuous control of his peritoneal sarcomatosis and developed no major additional side effects. Eleven months later (3 years after treatment initiation), he complained about right upper quadrant abdominal pain. Ultrasound and CT scan detected a new peritoneal metastasis impressing the liver (**Figure 11**). Biopsy of this lesion again confirmed a spindle-cell GIST, and molecular pathology now showed another new mutation in *KIT* exon 17, a point mutation (D820Y) clearly different from the 2 mutations detected earlier. (Mutational analysis performed and data provided by Eva Wardelmann, Department of Pathology, University of Bonn, Germany.) The patient withheld consent for another resection. Instead, he underwent an interstitial radiotherapy (at a high dose of 65 Gy).

Figure 11. CT Scan Showing a New Peritoneal Metastasis



Eleven months later, 3 years after initiation of imatinib therapy, ultrasound controls and CT scan detected a new peritoneal metastasis at the right upper quadrant impressing the liver. Molecular pathology at this time revealed another mutation in *KIT* exon 17 (D820Y). Figure provided courtesy of Peter Hohenberger, MD.

Outcome: The metastasis responded well to radiotherapy and no major problem arose locally. However, 9 months later, the patient developed multiple new progressive lesions in the abdomen

with no possibility of surgical resection. He finally succumbed to his disease in July 2005.

Discussion

This case demonstrates that even a patient with widespread abdominal sarcomatosis of GIST can be controlled with long-term imatinib therapy. Our patient showed a deletion of codons 552 to 557.¹¹ However, there is always a risk of developing new exon mutations, resulting in progression of already known but “silent” tumor nodules. Frequently, these nodules have stopped responding to imatinib treatment. In patients otherwise responsive to imatinib treatment, newly detected mutations can be found at *KIT* exons 13, 14, and 17.³² It is not fully understood why tumors without detectable signs of proliferation develop new mutations. If this is a random process, it would be wise to remove as much tumor as possible from the abdominal cavity during any laparotomy for the primary tumor or any subsequent procedure.

Imatinib remains the cornerstone of therapy in metastatic GIST with single progressive lesions. However, surgery should always be considered if resistant foci can be completely resected, as in this case. Surgical excision after a period of imatinib therapy for metastatic disease falls within the conventional indications for imatinib in Europe and the United States.^{1,22} Anterior resection, liver resection, and resection of peritoneal deposits are safe procedures with low morbidity and mortality if they can completely remove the only progressive lesion in an otherwise responsive GIST.²⁴ No clinical studies have investigated the effect of imatinib treatment interruption for surgery. The authors of this case recommend that discontinuation of imatinib therapy for the operative procedure not exceed 2 weeks, starting approximately 3 days before surgery if there are no signs of hyperfibrinolysis (elevated D-dimers).

Analysis of the molecular pathology of the primary tumor and mutational analysis of progressive lesions are crucial steps in identifying candidates for surgical resection. They provide information predictive of whether or not a tumor is likely to respond to other tyrosine kinase inhibitors. If focal lesions cannot be resected and progression continues, or if the patient’s condition does not allow a more extensive surgical approach, consider addition of a second agent as new *KIT* tyrosine kinase inhibitors become available (eg, sunitinib). ■



UNRESECTABLE GIST WITH IMATINIB TREATMENT INTERRUPTION

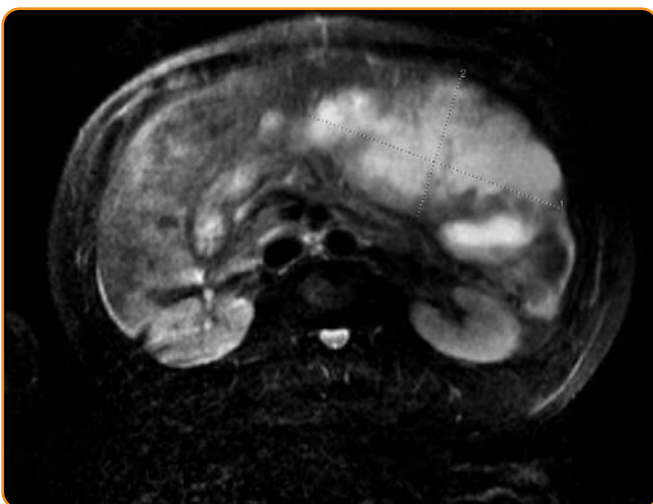
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This case illustrates the potentially negative effect of treatment interruptions in GIST patients treated with imatinib.

Case Presentation

Case history: In March 2001, a 55-year-old black African male patient experienced early satiety, feelings of intra-abdominal pressure, and weight loss. Ultrasound and CT scan performed in July of that year revealed an intra-abdominal mass. Exploratory laparotomy with biopsy revealed a large unresectable tumor, suspected to be in the stomach. Histologic analysis identified a spindle cell GIST strongly expressing CD117 and CD34; mitotic count was high: 59 mitoses/10 HPF. An MRI scan of the abdomen in August identified a 15 cm × 8 cm GIST in the upper abdomen (**Figure 12**).

Figure 12. MRI Scan Showing an Upper-Abdominal GIST

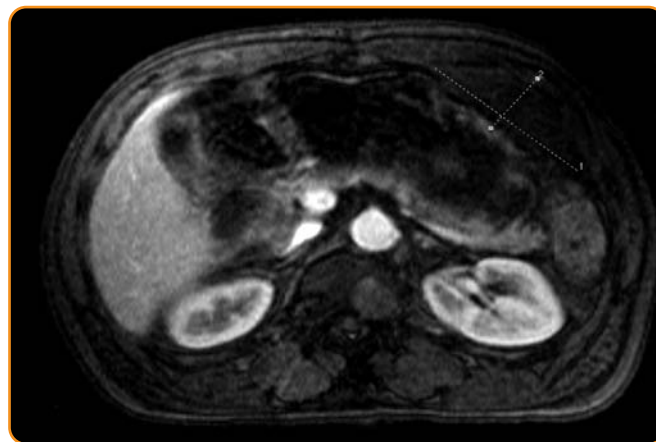


This baseline MRI scan was obtained in August 2001, before the patient enrolled in the European EORTC 62005 phase 3 trial of imatinib in advanced GIST, which compared initial doses of 400 or 800 mg/d. Upon entry, the patient was randomly assigned to treatment with 800 mg of imatinib daily. Figure provided courtesy of Peter Reichardt, MD, PhD.

Imatinib therapy: The patient was enrolled in a randomized phase 3 trial, EORTC 62005. Imatinib therapy was initiated at 800 mg/d in August 2001. An MRI scan of the abdomen in October 2001 showed reduced contrast enhancement but no change in tumor size. A follow-up MRI scan obtained in December 2001 showed that the tumor had regressed to 10 cm × 4 cm, with cystic degeneration (**Figure 13**).

In February 2002, an MRI scan of the abdomen revealed stable disease, confirmed by a follow-up abdominal MRI scan in May 2002.

Figure 13. Follow-up MRI Scan Showing Decreased GIST Size



An MRI scan obtained in December 2001, after approximately 4 months of treatment with imatinib 800 mg/d in EORTC study 62005, showed reduction in the dimensions of the patient's tumor. Figure provided courtesy of Peter Reichardt, MD, PhD.

Cessation of imatinib therapy: In June 2002, the patient experienced intravitreal hemorrhage. Imatinib therapy was stopped.

Surgery: In July 2002, a PET scan and tracer enhancement showed no pathologic findings. Multivisceral tumor resection was performed in July 2002, at the time of best response. Pathologic findings included an 11 cm × 5 cm × 3 cm tumor and several polypoid tumor knots ≤2 cm, showing largely fibrotic degeneration and low cell density. After 10 months of imatinib therapy (from August 2001 to June 2002), the histologic diagnosis was GIST of the stomach with >90% regressive alterations and peritoneal metastasis with extensively regressive alterations. Restarting imatinib was clearly indicated after surgery, but the patient refused because of skin discoloration, which resolved when imatinib was discontinued. As a black African, lightening of his skin color was an unacceptable side effect for him.

Imatinib therapy restarted: In November 2002, an MRI scan of the abdomen showed multiple peritoneal metastases. Imatinib therapy was restarted at 400 mg/d because the patient refused to return to the 800 mg/d dose, which he had tolerated well. Skin discoloration recurred. In March 2003, the patient developed severe mucositis. Imatinib therapy was stopped for 1 month and restarted in April at 300 mg/d.

Disease progression: Staging in July 2003 showed minimal tumor regression (no details available). In November 2003, however, staging revealed tumor progression (no details available). The patient's imatinib dose was increased to 600 mg/d. In February 2004, CT scan of the abdomen and pelvis revealed further tumor progression. The patient's imatinib dose was increased to 800 mg/d.

Investigational therapy: A CT scan of the abdomen and pelvis taken in March 2004 showed progressive disease with pleural effusion. At that time, the patient was given investigational therapy. By November 2004, the patient had again developed progressive disease, as shown on a CT scan of the abdomen and pelvis.

Outcome: In March 2005, the patient died of progressive disease.

Discussion

This patient was initially treated with imatinib 800 mg/d in a clinical trial setting. However, imatinib 400 mg once daily (QD) is considered the standard starting dose for patients with unresectable and/or metastatic GIST.²¹ In 2 clinical studies (study B2222

and an intergroup study S0033), the daily dose of imatinib was escalated to 800 mg in patients progressing at the lower daily doses of 400 mg or 600 mg.²¹ The daily dose was escalated to 800 mg in a total of 103 patients; 6 patients achieved a partial response and 21 patients achieved stabilization of their disease after dose escalation for an overall clinical benefit of 26%. From the safety data available, escalating the dose to 800 mg daily in patients progressing at lower doses of 400 mg or 600 mg daily does not seem to affect the safety profile of imatinib.

At present, standard treatment of advanced GIST is continuous administration of imatinib, with no upper limit of treatment duration. If possible, imatinib should be administered continuously without planned interruptions.³⁴

Because of adverse events, however, this patient experienced 2 imatinib treatment interruptions. In June 2002, imatinib therapy (800 mg/d) was stopped when the patient developed intravitreal hemorrhage. Because of skin discoloration, unacceptable to him as a black African, the patient refused to resume imatinib therapy after surgery in July 2002. Imatinib therapy (400 mg/d) was restarted in November 2002 after disease recurrence. In March 2003, the patient developed severe mucositis, and imatinib therapy was again stopped; 1 month later it was restarted at a reduced dosage, 300 mg/d.

As the patient's GIST continued to progress on standard imatinib therapy, he was treated with investigational therapy. In March 2005, however, he died of progressive disease. ■



ASSESSMENT AND MONITORING OF A TUMOR WITH INCONSISTENT RESPONSE TO IMATINIB

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Some patients show inconsistent response to imatinib, with some tumors responding and others failing to respond, posing unique challenges to the treatment team. This case illustrates the successful role of surgery and an increased imatinib dose (600 mg/d) in stabilizing the patient's disease.

Case Presentation

Case history: In June 2003, a 67-year-old male patient was admitted to the hospital complaining of asthenia, 4-kg weight loss, and anemia (hemoglobin level of 8.9 g/dL) over the course of 1 month. The patient had a medical history of liver steatosis, gastroesophageal bleeding, and colitis polyps.

Diagnosis: An abdominal CT scan exhibited at least 10 liver lesions; 3 were necrotic (**Figure 14**). The largest was a 10-cm lesion in the right segment of the liver. Colonoscopy revealed a 3- to 4-mm polyp (not observed on biopsy) and no other lesions until the cecum. Gastrosocopy showed reactive antral gastritis and mucosal atrophy with intestinal metaplasia. The primary tumor was not found. Biopsy of the liver lesions confirmed the diagnosis of a KIT-positive GIST.

Imatinib therapy: Two weeks later (June 12, 2003), the patient was entered into a clinical trial and started on imatinib therapy at 400 mg daily. Before starting treatment, the patient complained of lower extremity pain due to deep-vein thrombosis, confirmed by Doppler ultrasound. This was treated with low-molecular-weight heparin (LMWH), taken simultaneously with imatinib.

After 2 weeks of imatinib therapy, the target liver lesions remained stable in volume, but they had decreased in contrast uptake by dynamic contrast-enhanced Doppler ultrasound (DCE-US) (40% below baseline). After 4 months of imatinib therapy, CT scan showed an increase (to 13 cm) of the largest necrotic lesion; all other nodules decreased in size and density. Meanwhile, after 3 months of LMWH therapy, the patient's thrombosis had completely resolved, and he was able to discontinue that therapy with no recurrence of symptoms and no significant treatment-related toxicity.

First treatment interruption: At 6 months of imatinib therapy, the patient complained of right-sided pain and grade 3 NCI common toxicity criteria (CTC) skin toxicity. At that time, CT scan showed another slight increase in the size of the largest right lobular lesion (to 15 cm), which remained totally necrotic (**Figure 15**), as did the other, smaller nodules. The patient developed painful fissures on his palms and the soles of his feet, paronychia, and right finger erysipelas, requiring treatment with antibiotics and topical drugs. Imatinib treatment was interrupted for approximately 2 months, until the toxicity resolved.

Figure 14. Abdominal CT Scan



The scan shows a 10-cm liver lesion and at least 9 smaller lesions. Figure provided courtesy of Axel Le Cesne, MD, and Angela Cioffi, MD.

Figure 15. Follow-up CT Scan



The right lobular lesion had increased to 15 cm and remained necrotic. Figure provided courtesy of Axel Le Cesne, MD, and Angela Cioffi, MD.

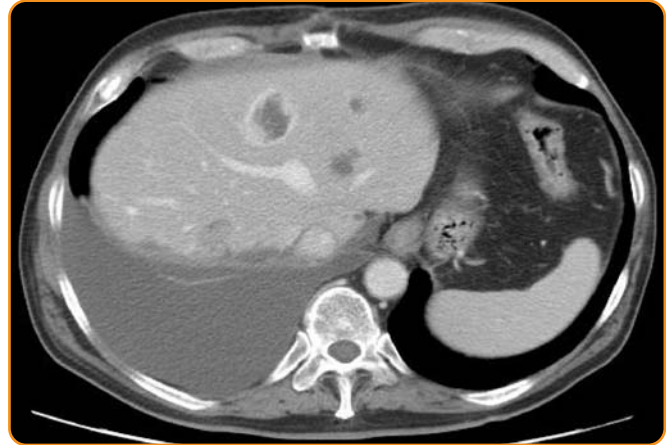
In February 2004, following treatment interruption, DCE-US showed a 100% contrast uptake in all initial target lesions. CT scan revealed that the huge necrotic mass had increased to 16 cm. Cutaneous toxicity had completely resolved by that time, and the patient restarted imatinib therapy, with no new episodes of cutaneous toxicity. After 1 year of treatment (June 2004), DCE-US again showed decreased uptake, but the largest lesion had continued to increase in size (to 19 cm).

First surgery: Although the surgeon had advised that a right hepatectomy with segment IV and a left radiofrequency would probably be incomplete, surgery became necessary because the patient's condition continued to degrade (right-sided pain and biliary compression of the mass, which had grown to 20 cm). In July 2004, the patient underwent a right hepatectomy enlarged to segment IV. The right lobe of the liver was totally involved by the huge liquefied mass. Histologic results showed the presence of many myxoid, hemorrhagic, and necrotic zones within the tumor, containing KIT-positive residual cells with 1 mitosis per 50 HPF. The same histologic findings appeared in 3 other nodules removed simultaneously. Because most of the nodules were not removed, this partial resection was classified as R2. Surgery was relatively well tolerated, with the exception of consistent peritumoral bleeding during surgery.

Imatinib treatment was interrupted 8 days before surgery and restarted 1 month later (August 2004) at the same daily dose, 400 mg/d. A CT scan taken before restarting therapy showed persistent left liver nodules. The largest was a 4.1-cm nodule in segment IV (**Figure 16**). A previously undetected 5.0-cm lesion of the small intestine was also visible. Over the next 14 months, both CT scans and ultrasound showed stable disease with no signs of activity at any level (**Figure 17**).

Second and third surgeries: By September 2005, the nodule located in liver segment IV had increased in volume, and it remained necrotic. Other nodules were unchanged, except the lesion in the small intestine, which had decreased in size (**Figure 18**). The surgeon recommended a new partial surgery, resection of both the intestinal and hepatic lesions. Unfortunately, just before the planned intervention, the patient experienced a digestive hemorrhage. Emergency resection of the small intestine was performed on October 4, 2005. Segmentectomy IV followed on January 13, 2006.

Figure 16. CT Scan Before Restarting Therapy



The scan revealed a 4.1-cm nodule in liver segment IV.
Figure provided courtesy of Axel Le Cesne, MD, and Angela Cioffi, MD.

Figure 17. CT Scan Showing Stable Disease



No signs of activity are visible at any level.
Figure provided courtesy of Axel Le Cesne, MD, and Angela Cioffi, MD.

Figure 18. CT Scan Taken in September 2005



The scan shows the decreased size of the small intestinal tumor.
Figure provided courtesy of Axel Le Cesne, MD, and Angela Cioffi, MD.

Imatinib treatment was interrupted for the operative procedures in a manner similar to the prior surgery.

This episode was considered a “second” partial resistance. Imatinib therapy was restarted at an increased dose (600 mg daily).

Outcome: At the time of this writing (April 2007), the patient is continuing imatinib therapy (600 mg daily). Since the second partial surgery, all other liver lesions have been completely controlled, and the patient is living a normal life.

Discussion

The patient presented initially with widespread disease, with no discernible primary lesion. He was entered into a clinical trial and started on imatinib therapy at 400 mg daily. Conforming to the protocol, the patient was seen every week for the first month, monthly until the sixth month, and subsequently every 3 months. DCE-US with perfusion software (Vascular Recognition Imaging) and contrast agent injection were used to predict tumor response before imatinib initiation, at days 1, 7, 14, 28, 56, and 84, and then every 3 months. Tumor assessment by CT scan was performed every 2 months.

From the outset, the patient demonstrated an inconsistent response to imatinib. The smaller lesions decreased in contrast uptake (at DCE-US) as well as in size and density, whereas the largest lesion failed to respond to therapy, doubling from 10 cm at presentation in June 2003 to 20 cm in July 2004, before the first surgical intervention. This inconsistent response (progression of the major lesion and stabilization of the other target lesions according to Response Evaluation Criteria for Solid Tumors) raised the question of optimal disease management. The continuing growth of the right liver lesion suggested partial resistance to imatinib. New therapeutic options were discussed: partial surgical procedures, chemoembolization, other interventional options, and/or inclusion of the patient in another trial with new targeted therapies.

If embolization of the lesions had been undertaken, it would have been performed by the radiologist because of the risk of weakening the remaining liver parenchyma or capsule; drainage or evacuation of the necrotic tumor could cause formation of cutaneous fistulas or rapid reconstitution of a hemorrhagic lesion. The surgeon advised that a right hepatectomy with segment IV and a left radiofrequency would probably be incomplete, with a high risk of post-resection hepatic failure. Nevertheless, with the patient’s condition continuing to degrade, a right hepatectomy enlarged to segment IV was performed in July 2004. Emergency resection of the small intestine followed a digestive hemorrhage in October 2005, and a third surgery (segmentectomy IV) was performed in January 2006. Because the last episode was considered a second partial resistance to imatinib, the patient’s dose was increased to 600 mg/d.

Treatment interruptions: The patient’s course of imatinib therapy was interrupted several times for adverse events, a factor associated with progressive disease.³⁵ At 6 months, grade 3 NCI-CTC skin toxicity necessitated the first dose interruption, for approximately 2 months. At the end of that time (February 2004), DCE-US showed a 100% contrast uptake (in all initial target lesions) and CT scan revealed that the large necrotic mass had increased to 16 cm. In July 2004, the patient underwent his first surgery, a right hepatectomy enlarged to segment IV. Imatinib therapy was discontinued 8 days before therapy and restarted 1 month later. Over the next 14 months, the patient achieved stable disease, but by September 2005, the nodule in liver segment IV had increased in size. Emergency resection of the small intestine in October 2005 and segmentectomy IV in January 2006 also necessitated interruption of imatinib therapy.

After the patient experienced a second partial resistance, imatinib therapy was restarted at an increased dose (600 mg daily) in accordance with the US and European guidelines.^{1,22,35} Since the second partial surgery, all other liver lesions have been completely controlled by imatinib therapy. ■

SUMMARY

This monograph illustrates several important points about the management of advanced GIST.

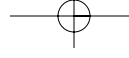
- Imatinib indication and dosing:** Imatinib is indicated for adult patients with KIT (CD117)-positive unresectable and/or metastatic malignant GIST.²¹ The 400-mg/d dose is considered the standard starting dose. It is recommended that imatinib be administered continuously without planned interruptions.
- The 64-month results of Study B2222:** In Study B2222, the median duration of response to imatinib was 27 months (data on file, Novartis Pharmaceuticals),^{17,18} and some patients continued to respond for 5 years or longer. Approximately 84% of patients experienced tumor control (objective tumor response or stable disease). The median onset of response was 13 weeks; however, for more than 25% of responding patients, response occurred more than 6 months after treatment initiation. Patients with stable disease achieved similar survival to those with a partial response, suggesting that lesion volume reduction in response to imatinib therapy may not be an important prognostic factor. Median overall survival was 58 months.¹⁷
- Assessment of response:** Response to imatinib may be indicated by decreased tumor density during therapy or low attenuation of the lesion on CT scan.^{14,20} Appearance of a new hypodense lesion (visible because of GIST cell apoptosis) does not indicate progression.²⁰
- Adverse event management:** Imatinib therapy requires close surveillance.²¹ The most frequent adverse effects ($\geq 10\%$ of patients) associated with imatinib are periorbital or leg edema, occasional muscle cramps, diarrhea, nausea or vomiting, fatigue, abdominal pain, muscle pain, and skin rash. Grades 1-2 thrombocytopenia, anemia, and neutropenia are also frequent. Elevation of serum transaminase levels occurs in $>1.0\%$ but $\leq 10\%$ of patients. Many side effects are mild to moderate in severity and tend to decrease over time, and thus may not require any specific therapy.¹⁶ Periorbital edema often responds to diuretics, and nausea may be alleviated when the daily imatinib dose is divided and administered BID. Reinstitution of therapy is the goal after treatment interruption for adverse events.
- Liver metastases:** Resection of liver metastases may be inappropriate if there has been only a short time between resection of the primary tumor and development of the metastases.²⁹
- Metastasectomy:** Complete metastasectomy before initiation of imatinib is of limited benefit versus imatinib therapy alone.³⁰
- Stable disease:** Stable disease is evidence of response to imatinib, but patients frequently expect tumor shrinkage. Patient education is essential in handling these situations. It is important to point out that overall survival is similar with stable disease or partial response.¹⁷
- Imatinib following resection of metastases:** Continuation of imatinib following surgical excision of overt metastases falls within the conventional indications for imatinib in Europe and the United States.^{1,22}
- Secondary resistance:** Many GIST patients with an excellent initial response to imatinib later develop acquired (secondary) resistance, defined as resistance occurring after the first 6 months of imatinib therapy.^{1,8} Imatinib dose escalation up to 800 mg/d is recommended whenever feasible in these patients.^{1,8} Imatinib treatment should probably be continued indefinitely in responding and stable patients. Surgery should be considered if resistant foci can be completely resected.^{1,22}
- Disease recurrence:** Recurrent disease can take the form of a new lesion at the site of surgical resection, an increase in size of an existing lesion, a new metastasis, or development of an intratumoral nodule ("nodule within a mass").¹ Resistant liver lesions often emerge within or at the border of a responding (hypodense) metastasis and can be seen as a node within a lesion upon imaging. Such nodules frequently harbor a secondary *KIT* mutation. When other metastatic lesions continue to respond, consider surgical resection of a growing single lesion (or a few such lesions). Radiofrequency ablation may be attempted when surgery is not feasible.¹

- ***Inconsistent response:*** Some patients show inconsistent response to imatinib, with only some tumors responding, posing unique challenges to the treatment team. Surgery and an increased imatinib dose may both have a role in stabilizing the patient's disease.
- ***Alternative tyrosine kinase therapy:*** Sunitinib malate has been approved for the treatment of patients with GIST whose disease has progressed or who are unable to tolerate treatment with imatinib. ■

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Released: May 2007
G-GLI-10095