NCCN Guidelines® Insights

Gastrointestinal Stromal Tumors, Version 2.2014

Featured Updates to the NCCN Guidelines

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common soft tissue sarcoma of the gastrointestinal tract, resulting most commonly from KIT or platelet-derived growth factor receptor α (PDGFRα)–activating mutations. These NCCN Guideline Insights highlight the important updates to the NCCN Guidelines for Soft Tissue Sarcoma specific to the management of patients with GIST experiencing disease progression while on imatinib and/or sunitinib. (J Natl Compr Canc Netw 2014;12:853–862)

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel’s discussion, including the literature reviewed.

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Learning Objectives:

Upon completion of this activity, participants will be able to:
• Integrate into professional practice the updates to NCCN Guidelines for Gastrointestinal Stromal Tumors
• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Gastrointestinal Stromal Tumors

http://education.nccn.org/node/46929; and 4) view/print certificate.

Gastrointestinal Stromal Tumors, Version 2.2014
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Overview

Soft tissue sarcomas (STS) are a heterogeneous group of rare solid tumors with distinct clinical and pathologic features. In 2014, an estimated 12,020 people will be diagnosed with STS in the United States, and approximately 4740 will die of the disease.1 Gastrointestinal stromal tumors (GIST) are the most common STS of the gastrointestinal tract, resulting most commonly from KIT or platelet-derived growth factor receptor α (PDGFRα)–activating mutations.2

Loss-of-function mutations in the succinate dehydrogenase (SDH) genes are among the most common genetic abnormalities found in wild-type GISTs.3–7 These mutations lead to the loss of the enzyme succinate dehydrogenase, which is critical for the Krebs cycle. The SDH complex is composed of four subunits: SDHA, SDHB, SDHC, and SDHD. Mutations in the SDHB subunit have been associated with a worse prognosis.8

The identification of these mutations is important for determining the risk of recurrence and metastasis, as well as for guiding treatment.9,10 Patients with wild-type GIST lacking KIT or PDGFRα mutations should be evaluated for germline mutations in the SDH genes.11 This may help identify individuals at risk for developing additional tumors or for having a more aggressive type of GIST.

NCCN Guidelines Insights

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
TREATMENT FOR PROGRESSIVE DISEASE

Continue with the same dose of imatinib and consider the following options for progressing lesions:
- 
  
  
  Reassess therapeutic response with CT
- 
  
  Dose escalation of imatinib as tolerated or
  
  Change to sunitinib (category 1)

For performance status (PS) 0-2:
- 
  
  Dose escalation of imatinib as tolerated or
  
  Change to sunitinib (category 1)

If disease is progressing despite prior imatinib or sunitinib therapy, consider the following options:
- 
  
  Regorafenib (category 1)
- 
  Clinical trial
- 
  Consider other options listed in SARC-E (based on limited data)
- 
  Best supportive care

**With GIST lacking KIT or PDGFRα mutations (see GIST-I and GIST-B, pages 855 and 857).**

The introduction of KIT and PDGFRα inhibitors such as imatinib and sunitinib has significantly improved the outcomes in patients with unresectable or metastatic GIST. Regorafenib, another multikinase inhibitor, was recently approved for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib.

These NCCN Guidelines Insights discuss the management of patients with GIST experiencing disease progression while on imatinib and/or sunitinib.

**GIST: Management of Progressive Disease**

**Resistance to Imatinib and Sunitinib**

Imatinib is the standard first-line therapy for patients with unresectable or metastatic GIST. In phase II and III studies, imatinib has resulted in high overall response rates and exceptionally good progression-free survival (PFS) in patients with unresectable and/or metastatic GIST, inducing objective responses in more than 50%. The presence and type of KIT or PDGFRα mutation status has been identified as the predictor of response to imatinib. In randomized clinical trials, the presence of a KIT exon 11 mutation was associated with better response rates, PFS, and overall survival (OS) than KIT exon 9 mutations or wild-type GISTs. The EORTC 62005 study group identified the presence of KIT exon 9 mutation as the strongest adverse prognostic factor for risk of progression and death. A meta-analysis of the EORTC 62005 and SWOG S0033/CALGB 150105 phase III trials that randomized 1640 patients with advanced GIST to standard-dose (400 mg/d) or high-dose imatinib (800 mg/d) showed a PFS benefit for patients with KIT exon 9 mutations treated with 800 mg of ima-
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**PRINCIPLES OF PATHOLOGIC ASSESSMENT FOR GIST**

- Pathologic assessment should follow the guidelines outlined in SARC-A.
- Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Several ancillary techniques are useful in support of GIST diagnosis, including immunohistochemistry (95% express CD117 and 80% express CD34, DOG1) and molecular genetic testing (for mutations in *KIT* or *PDGFRα*). DOG1 immunostaining may be useful for cases that cannot be categorized as GIST based on CD117 immunostaining. Referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.
- Tumors lacking *KIT* or *PDGFRα* mutations should be considered for further evaluations such as staining for SDHB by immunohistochemistry, BRAF mutation analysis and SDH gene mutation analysis.
- Tumor size and mitotic rate are used as guides to predict the malignant potential of GISTs, although it is notoriously difficult to predict the biologic potential of individual cases. The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 5 mm² of tissue.
- Approximately 80% of GISTs have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5%-10% of GISTs have a mutation in the gene encoding the related *PDGFRα* receptor tyrosine kinase. Since about 10%-15% of GISTs have no detectable *KIT* or *PDGFRα* mutation, the absence of a mutation does not exclude the diagnosis of GIST. The presence and type of *KIT* and *PDGFRα* mutations are not strongly correlated with prognosis.
- The mutations in *KIT* and *PDGFRα* in GIST result in expression of mutant proteins with constitutive tyrosine kinase activity. If tyrosine kinase inhibitors are considered as part of the treatment plan, genetic analysis of the tumor should be considered since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRα* genes is correlated with response (or lack of a response) to specific tyrosine kinase inhibitors. However, the type of mutation cannot be accurately predicted based on the anatomic site of origin or histopathologic features.
- In patients with advanced GISTs, approximately 90% of patients benefit from imatinib when their tumors have a *KIT* exon 11 mutation; approximately 50% of patients benefit from imatinib when their tumors harbor a *KIT* exon 9 mutation, and the likelihood of response improves with the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the *PDGFRα* gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of *KIT* and *PDGFRα* mutations, only a subset of patients with advanced GISTs benefit from imatinib. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRα*. Sunitinib treatment is indicated for patients with imatinib-resistant tumors, or imatinib intolerance. Regorafenib is indicated for patients with disease progression on imatinib and sunitinib.

Although imatinib benefits most patients with advanced GIST, some develop resistance to the drug. Primary resistance is defined as the evidence of clinical progression developing during the first 6 months of imatinib therapy, and is most commonly seen in patients with *KIT* exon 9 mutations treated with imatinib at 400 mg/d or patients with *PDGFRα* exon 18 D842V mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRα*, most of which are SDH-deficient GIST. Secondary resistance is seen in patients who have been on imatinib for more than 6 months with an initial response or disease stabilization followed by progression, most commonly because of the outgrowth of tumor clones with secondary mutations in *KIT*. Dose escalation to 800 mg/d or switching to sunitinib is a reasonable option for patients experiencing disease progression on imatinib at 400 mg/d. Sunitinib is a multikinase inhibitor active against a variety of tyrosine kinases, including KIT, PDGFR, and vascular endothelial growth factor receptor (VEGFR). In randomized clinical studies, sunitinib has resulted in a significant improvement in median time to progression and a significantly greater estimated OS in patients with imatinib-resistant GIST compared with placebo. Heinrich et al reported that sunitinib induced higher response rates in patients with primary *KIT* exon 9 mutations than those with...
KIT exon 11 mutations (58% vs 34%, respectively). PFS and OS were significantly longer for patients with KIT exon 9 mutations or wild-type GIST compared with those with KIT exon 11 mutations. Only 4 patients had PDGFRα mutations; of these, 2 had a primary and 1 a secondary D842V mutation and did not experience response to treatment. In patients with KIT exon 11 mutations, PFS and OS were longer for those with secondary exon 13 or 14 mutations compared with those with exon 17 or 18 mutations. Additional studies are needed to confirm these findings.

Comprehensive molecular studies investigating the mechanisms of resistance to sunitinib are limited because of the small number of patients who are surgical candidates after failure of 2 tyrosine kinase inhibitors (TKI) therapies. Nevertheless, available evidence (both clinical and preclinical) indicates that although sunitinib is very sensitive to ATP-binding pocket mutations that confer resistance to imatinib, it has little activity against other imatinib-resistant mutations in the KIT activation loop.26–28

### Management of Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against KIT, PDGFR, and VEGFR, was recently approved by the FDA for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib. A phase III study randomized 199 patients with metastatic and/or unresectable GIST experiencing disease progression on prior therapy with imatinib and sunitinib to either regorafenib (n=133) or placebo (n=66).29 The median PFS (4.8 vs 0.9 months; P<.001) and disease control rate (53% vs 9%) were significantly higher for regorafenib compared with placebo. The PFS rates at 3 and 6 months were 60% and 38%, respectively, for regorafenib compared with 11% and 0%, respectively, for placebo. The
hazard ratio for OS was 0.77, with 85% of patients in the placebo arm crossing over to regorafenib because of disease progression. The most common treatment-related adverse events (≥ grade 3) were hypertension (23%), hand-foot skin reaction (20%), and diarrhea (5%).

Sorafenib, nilotinib, dasatinib, and pazopanib have also shown activity in patients with GIST resistant to imatinib and sunitinib. Much of the data on these TKIs are from phase II studies and retrospective analyses involving small numbers of patients.

In a prospective multicenter phase II study of 38 patients with unresectable KIT+ GIST that had progressed on imatinib and sunitinib, sorafenib resulted in a disease control rate of 68% (55% of patients had stable disease and 13% had a partial response). Median PFS and OS were 5.2 and 11.6 months, respectively; 1- and 2-year survival rates were 50% and 29%, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, sorafenib also demonstrated activity, resulting in a median PFS and OS of 6.4 and 13.5 months, respectively. Notably, patients included in this study had not been treated with regorafenib, and the efficacy of sorafenib following regorafenib therapy in patients with metastatic GIST resistant to imatinib and sunitinib has not been studied.

In a retrospective analysis of 52 patients with advanced GIST resistant to imatinib and sunitinib, nilotinib resulted in response and disease control rates of 10% and 37%, respectively. Median PFS and OS were 12 and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy and best supportive care (with or without a TKI) in patients who were resistant or intolerant to imatinib and sunitinib (248 patients), the PFS associated with nilotinib was not found to be superior to best supportive care (109 vs 111 days; \( P = 0.56 \)). In a post hoc subset analysis, patients experiencing progression on both imatinib and sunitinib who had not received any other therapy had an improved OS (>4 months) with nilotinib compared with best supportive care (205 vs 280 days; \( P = 0.02 \)). The clinical benefit associated with nilotinib may be specific to subsets of patients with KIT exon 17 mutations, previously treated with imatinib and sunitinib.

Dasatinib has demonstrated activity against the PDGFRα D842V mutation that confers the highest resistance to imatinib, and it could be an effective treatment option for this group of patients with imatinib-resistant GIST. In the phase II study of 50 patients with advanced GIST resistant to imatinib, dasatinib was associated with a median PFS and OS of 2 and 19 months, respectively, with response assessment based on Choi criteria. Median PFS for patients with wild-type GIST was 8.4 months.

Pazopanib has also shown marginal activity in heavily pretreated patients with advanced GIST. In a prospective multicenter phase II study of patients with advanced GIST following failure of at least imatinib and sunitinib (n=25), pazopanib was well tolerated, resulting in stable disease in 48% of patients, with a 24-week nonprogression (complete response + partial response + stable disease) rate of 17%. The median PFS and OS were 1.9 and 10.7 months, respectively.

**NCCN Recommendations**

Dose escalation of imatinib up to 800 mg/d (given as 400 mg twice daily) as tolerated or switching to sunitinib (category 1) are included as options for patients experiencing progressive disease (limited disease or widespread systemic disease in patients with good performance status) on standard-dose imatinib (see GIST-7, page 856). All clinical and radiologic data, including lesion density on CT and patient compliance to treatment with standard-dose imatinib, should be assessed before dose escalation of imatinib or switching to sunitinib.

For patients with limited progressive disease on standard-dose imatinib, second-line therapy with sunitinib should be initiated only if most of the disease is no longer controlled by imatinib; consideration of other therapeutic interventions for progressing lesions is warranted. Surgical resection should be considered in carefully selected patients with limited progressive disease that is potentially easily resectable. However, incomplete resections are frequent, with high complication rates. The guidelines have included, only for patients with limited progressive disease, continuation of imatinib at the same initial dose and treatment of progressing lesions with resection or radiofrequency ablation or chemembolization or palliative RT (for rare patients with bone metastases) as an option.

Reorafenib (category 1) is recommended for patients experiencing disease progression on imatinib and sunitinib. Based on the limited data,
the NCCN Guidelines have also included sorafenib, dasatinib, and nilotinib as additional options for patients who are no longer receiving clinical benefit from imatinib, sunitinib, or regorafenib (see SARC-E, page 858), although all data regarding the potential benefit of these agents are from the pre-regorafenib era.

In patients with progressive disease no longer receiving benefit from current TKI therapy, reintroduction of previously tolerated and effective TKI therapy for palliation of symptoms can be considered (see GIST-7, page 856). The results of a recent randomized study showed that imatinib rechallenge significantly improved PFS and disease control rate in patients with advanced GIST after failure of at least imatinib and sunitinib. However, the duration of survival benefit was brief because of continued progression of TKI-resistant clones.

Any patient who experiences disease progression despite prior therapy or who has a recurrence, regardless of presentation, should be considered a candidate for enrollment in a clinical trial, if an appropriate trial is available.

### Continuation of TKI Therapy

The optimal duration of TKI therapy in patients with responding or stable disease is not known. The results of a prospective, multicenter, randomized phase III study (BFR14) showed a significant increase in the rate of disease progression when imatinib was interrupted in patients with advanced disease who were stable or responding to imatinib. A recent report from this study confirmed that patients with rapid disease progression after interruption of imatinib had a poorer prognosis. More importantly, the quality of response on reintroduction of imatinib did not reach the tumor status observed at randomization.

The panel strongly recommends that TKI therapy at the prescribed daily dose should be continued as long as patients are experiencing clinical benefit (response or stable disease). The panel also feels that continuation of TKI therapy lifelong for palliation of disease progression after interruption of imatinib had a poorer prognosis. More importantly, the quality of response on reintroduction of imatinib did not reach the tumor status observed at randomization.

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### Summary

GIST is the most common STS of the gastrointestinal tract, resulting most commonly from KIT- or PDGFRA-activating mutations. TKI therapy with imatinib, sunitinib, and regorafenib has emerged as an effective treatment option for patients with unresectable or metastatic GIST. Dose escalation of imatinib up to 800 mg/d as tolerated or switching to sunitinib are included as options for patients with progressive disease on standard-dose imatinib. Regorafenib is recommended for patients experiencing disease progression while on imatinib and sunitinib. TKI therapy at the prescribed daily dose should be continued as long as patients are receiving clinical benefit (response or stable disease).

### References

11. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic...


In the NCCN Guidelines for patients with GIST progressing on standard-dose imatinib?

1. Which of the following are included as treatment options in the NCCN Guidelines for patients with GIST progressing on standard-dose imatinib?
   a. Dose escalation of imatinib up to 800 mg/d as tolerated
   b. Switching to sunitinib
   c. Continuation of imatinib at the same initial dose and treatment of progressing lesions with other therapeutic interventions
   d. All of the above

2. Regorafenib is recommended for patients with GIST experiencing disease progression while on imatinib and sunitinib.

3. Which of the following mutations is associated with better clinical outcomes in patients with unresectable or metastatic GIST treated with standard-dose imatinib?
   a. KIT exon 9
   b. KIT exon 11
   c. PDGFRα D842V
   d. All of the above