Abstract

The major changes to the 2012 and 2011 NCCN Guidelines for Soft Tissue Sarcoma pertain to the management of patients with gastrointestinal stromal tumors (GISTs) and desmoid tumors (aggressive fibromatosis). Postoperative imatinib following complete resection for primary GIST with no preoperative imatinib is now included as a category 1 recommendation for patients with intermediate or high risk of recurrence. The panel also reaffirmed the recommendation for preoperative use of imatinib in patients with GISTs that are resectable with negative margins but associated with significant surgical morbidity. Observation was included as an option for patients with resectable desmoid tumors that are small and asymptomatic, not causing morbidity, pain, or functional limitation. Sorafenib is included as an option for systemic therapy for patients with desmoid tumors. (JNCCN 2012;10:951–960)

Please Note

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, resulting from activating mutations in one of the receptor protein tyrosine kinases, KIT (CD117) or platelet-derived growth factor receptor alpha (PDGFRα). Most GISTs (80%) are KIT-positive, and 5% to 10% have mutations in the PDGFRA gene and express little or no KIT. Approximately 10% to 15% of GISTs have no detectable KIT or PDGFRA mutations (wild-type GIST). Recent studies have identified several germline mutations in the succinate dehydrogenase subunit in patients with wild-type GIST. Therefore, the absence of KIT or PDGFRA mutations does not exclude the diagnosis of GIST. In addition to morphologic diagnosis, ancillary techniques, including immunohistochemistry and molecular genetic testing, would be beneficial to confirm the diagnosis of GIST. The introduction of imatinib, an inhibitor of multiple receptor tyrosine kinases including KIT,
Management of GISTs

Preoperative Imatinib

RTOG 0132/ACRIN 6665 is the first prospective study that evaluated the efficacy of preoperative imatinib (600 mg/d) in patients with potentially resectable locally advanced primary GISTs (intermediate-to-high-risk; n = 30) or metastatic/recurrent disease (n = 22). Patients experiencing partial response or stable disease after preoperative imatinib underwent resection and continued imatinib postoperatively for 2 years. Among patients with primary GISTs, partial response and stable disease after preoperative imatinib were observed in 7% and 83%, respectively. In patients with recurrent or metastatic GIST, progression-free survival has significantly improved the outcome in patients with unresectable and/or metastatic disease. Several prospective studies have also evaluated the efficacy of imatinib in the preoperative and postoperative setting to further improve outcomes after complete resection.

Desmoid tumors, also known as aggressive fibromatoses, are unique mesenchymal neoplasms, and are often considered “benign malignancies.” Specifically, these tumors are an aggressive fibroblastic proliferation of well-circumscribed, locally invasive, differentiated fibrous tissue and are often categorized as low-grade sarcomas because of their high tendency to recur locally after excision. Desmoid tumors can cause functional morbidity and also have a high recurrence rate. Although desmoid tumors are often locally invasive, they rarely metastasize and have a good prognosis.

These NCCN Guidelines Insights include the major discussion points corresponding to the updates in the 2012 and 2011 guidelines.
(PFS) rates were 83% and 77%, respectively. In this study, among patients with primary resectable GIST, R0 resection (complete removal of all gross and microscopic disease) was performed in 77% of patients, and partial organ-preserving and function-preserving surgery was reported in most of these cases. However, survival benefit could not be determined because all patients received postoperative imatinib for 2 years.

In another prospective study, Fiore et al. reported that preoperative imatinib improved resectability and reduced surgical morbidity in patients with primary GISTs that were resectable through a major surgical procedure associated with significant surgical morbidity or those with unresectable GISTs. The median size reduction was 34% and the estimated 3-year PFS rate was 77%. Imatinib was continued postoperatively for 2 years in all patients.

In the subgroup analysis of patients with nonmetastatic locally advanced primary GIST treated with imatinib in the prospective BFR14 phase III trial, preoperative imatinib was associated with a partial response rate of 60% (15 of 25 patients); 36% (9 of 25 patients) of these patients underwent surgical resection of the primary tumor after a median of 7.3 months of preoperative imatinib; the 3-year PFS and OS rates for patients who underwent resection were 67% and 89%, respectively. All patients who underwent resection were treated with postoperative imatinib.

The optimal duration of preoperative imatinib remains unknown. In the RTOG 0132 study, preoperative imatinib was administered for 8 to 12 weeks followed by resection in patients with responding or stable disease. In other studies, preoperative imatinib was administered for 7 to 9 months. A small prospective trial (19 patients) reported a response rate of 70% after 3 to 7 days of preoperative imatinib (600 mg/d) in patients undergoing surgical resection for primary or recurrent GISTs. However, results showed no histologic evidence of cytoreduction within 3 to 7 days of preoperative imatinib.
**NCCN Recommendations:** Surgery is the primary treatment for patients with primary localized GISTs (≥ 2 cm) that are potentially resectable without significant risk of morbidity (see GIST-3, on page 952). The goal of surgical treatment is to achieve complete gross resection with negative microscopic margins and minimal surgical morbidity. Preoperative imatinib should be considered if surgical morbidity could be improved by reducing the tumor size before resection. In prospective studies, preoperative imatinib has been tested at a daily dose of either 400 or 600 mg. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Soft Tissue Sarcoma recommend an initial dose of 400 mg/d (to view the full guidelines, visit NCCN.org). Patients with documented KIT exon 9 mutations may benefit from dose escalation up to 800 mg/d (given as 400 mg twice daily), as tolerated (see GIST-D, on page 956). Collaboration between the medical oncologist and surgeon is necessary to determine the appropriateness of surgery in patients experiencing a major response or stable disease after receiving preoperative imatinib.

Preoperative imatinib is recommended as primary treatment for patients with GIST that is resectable with negative margins but with a risk of significant morbidity (see GIST-4, on page 953). However, the patient may proceed to surgery if bleeding or symptomatic. The NCCN Guidelines recommend continuation of preoperative imatinib until maximal response (defined as no further improvement or stable disease after receiving preoperative imatinib). Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

Imatinib is recommended as primary treatment for patients with definitively unresectable, recurrent, or metastatic disease (see GIST-5, on page 954). Data from retrospective studies have shown that surgery following imatinib may be beneficial in selected patients with recurrent or metastatic GIST.
Prospective phase III trials are underway to assess whether surgical resection improves clinical outcome in patients with resectable metastatic GIST responding to tyrosine kinase inhibitor therapy. The guidelines recommend that response be assessed within 3 months of initiating imatinib to determine whether the GIST has become resectable. In selected patients, imaging can be performed before 3 months. At this time, continuation of imatinib is recommended until progression, if resection is not feasible, for all patients with unresectable, recurrent, or metastatic GIST.

Postoperative Imatinib

In the single-arm multicenter Intergroup phase II ACOSOG Z9000 trial, postoperative imatinib for 1 year after complete resection prolonged relapse-free survival (RFS) and improved OS in patients with primary localized GISTs at high risk of recurrence compared with historical controls. These findings were confirmed in a subsequent double-blind randomized phase III trial (ACOSOG Z9001), which randomized patients with primary localized GISTs (≥ 3 cm) to postoperative imatinib at 400 mg (359 patients) or placebo (354 patients) for 1 year after complete resection. At a median follow-up of 19.7 months, the estimated RFS rate at 1 year was significantly higher in the imatinib arm compared with the placebo arm (98% vs. 83%, respectively; P < .001). No difference in OS was seen between the arms (99.2% vs. 99.7%, respectively; P = .47). In the subset analysis, RFS statistically favored the imatinib arm in patients with intermediate-risk (≥ 6 cm and < 10 cm; 98% vs. 76% for placebo; P = .05) and high-risk tumors (≥ 10 cm; 77% vs. 41% for placebo; P < .0001).

The results of the recently completed Scandinavian Sarcoma Group XVIII trial (SSGXVIII/AIO) suggest that postoperative imatinib administered for 36 months improves RFS and OS compared with 12 months in patients with a high-risk of recurrence after surgery.

Imatinib should be taken with a low fat meal and a large glass of water.
high-risk of recurrence after surgery (tumor size > 10 cm or tumor with a mitotic rate of > 10 mitoses/50 high-power field [HPF] or tumor size > 5 cm and a mitotic rate of > 5 mitoses/50 HPF or tumor rupture) to either 12 months (n = 200) or 36 months (n = 200) of postoperative imatinib. At a median follow-up of 54 months, the RFS and OS rates were higher in the 36-month group compared with the 12-month group (5-year RFS: 66% vs. 48%, respectively; \( P < .0001; \) 5-year OS: 92% vs. 82%, respectively; \( P = .019 \)).

**NCCN Recommendations:** Although complete resection is possible in approximately 85% of patients with primary tumors, many patients will develop recurrence after complete resection, and the 5-year survival rate is approximately 50% for patients with recurrent disease.\(^{21-23}\) In randomized studies, postoperative imatinib has been associated with improved RFS after complete resection without prior imatinib.\(^{19,20}\)

Estimation of risk of recurrence is important in selecting patients who would benefit from post-operative imatinib after complete resection. In the ACOSOG Z9001 trial, risk stratification was based on tumor size, and postoperative imatinib improved RFS in patients with GISTs 3 cm or larger, but it was statistically significant in patients with intermediate (≥ 6 cm and < 10 cm) and high risk (> 10 cm) of recurrence.\(^{19}\) In the SSGXVIII/AIO trial, risk stratification was based on tumor size, site, mitotic count, and rupture; survival benefit was seen in patients with high-risk of recurrence (mitotic count > 5 mitoses/50 HPF; size > 5 cm; nongastric location; and tumor rupture).\(^{20}\)

Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.\(^{24,25}\) Based on results of the ACOSOG Z9001 trial and the recently completed randomized SSGXVIII/AIO trial, the NCCN Guidelines recommend postoperative imatinib (400 mg; category 1) after complete resection of primary GIST with no preoperative imatinib in patients with intermediate or high risk of recurrence.

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**NCCN Guidelines Insights**

**Soft Tissue Sarcoma, Version 2.2012**

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**PRIMARY TREATMENT**

- **Resectable**
  - Surgery\(^d\) and/or RT\(^g,h\) and/or Systemic therapy\(^i\)
  - Treatmand
- **Observation**
- **Stable**
- **Progression**

**FOLLOW-UP**

- **R0** or Complete radiographic response
  - Observation
  - Consider postoperative RT\(^b\) if large tumor
- **R1** or Minimal residual disease
  - Consider resection of RT\(^b\), if no prior RT or Observation
  - Definitive RT\(^g\) or Systemic therapy\(^i\)
  - Radical surgery to be considered if other modalities fail
  - Observation
- **R2** or Gross residual disease
  - Observation
  - Consider postoperative RT if large tumor

**DESM-2**

\(^{d}\)For tumors that are symptomatic, or impairing or threatening function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.

\(^{e}\)For desmoids, microscopic positive margins are acceptable if achieving negative margins would produce excessive morbidity.

\(^{f}\)See Principles of Systemic Therapy (SARC-E).

\(^{g}\)RT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk or head and neck.

\(^{h}\)Dose of definitive RT without surgery: 54-58 Gy in the absence of any prior radiation therapy.

The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST (tumor > 5 cm in size and a mitotic rate > 5 mitoses/50 HPF).

For patients who have undergone complete resection after preoperative imatinib, the panel agreed that continuation of imatinib (at the same dose that induced objective response) following resection is warranted (see GIST-6, on page 955). The panel acknowledged that although data from single- and multi-institutional trials support the benefit for continuation of postoperative imatinib for 2 years after surgery,\textsuperscript{10-13} the exact duration of postoperative imatinib in this group of patients has not been studied in randomized trials. The panel emphasizes that preoperative imatinib may prohibit accurate assessment of recurrent risk.

In patients with persistent gross residual disease (R2 resection), the guidelines recommend that postoperative imatinib be considered for all patients, including those who have received preoperative imatinib (see GIST-6, on page 955). Additional resection may be considered to remove residual disease. Imatinib treatment should be continued following re-resection, regardless of surgical margins, until progression.

### Desmoid Tumors (Aggressive Fibromatoses)

**“Wait and See” Approach for Selected Patients With Resectable Tumors**

Surgery is the primary treatment for patients with resectable desmoid tumors.\textsuperscript{26} The results of recent retrospective analyses suggest that observation may be appropriate for select patients with resectable tumors (small size, asymptomatic, and tumors located at sites where increase in size will not alter the outcome of surgery).\textsuperscript{27-29} In a retrospective analysis of patients with desmoid fibromatoses (74 with primary tumor and 68 with recurrence), Fiore et al.\textsuperscript{29} reported that...
the 5-year PFS rates for patients with primary tumors were 47% for those who were treated with a “wait and see” approach (no surgery or radiation therapy) and 54% for those who received chemotherapy or hormonal therapy ($P = .70$).\(^2\) The corresponding survival rates were 54% and 61% ($P = .48$), respectively, for patients with recurrence. Large tumors (> 10 cm) and tumors located on the trunk were associated with high risk of recurrence.

**NCCN Recommendations:** In the 2011 NCCN Guidelines for Soft Tissue Sarcoma, based on these results, the panel discussed including observation as an option for patients with resectable tumors (see DESM-2, on page 957). However, some panel members were not in favor of including observation (until progression) as the initial treatment option preceding surgery for all patients with resectable disease. They felt that delaying surgery until after documented progression will make the tumor not amenable to resection. In addition, the panel also felt that patients with symptomatic or function-impairing tumors should be offered appropriate intervention (surgery, systemic therapy, or radiation therapy) as an initial treatment depending on the tumor location and potential morbidity. The panel concluded that patients with desmoid tumors can be managed appropriately with a careful “wait and see” approach if their tumors are asymptomatic and not located in an area that could lead to functional limitations if the tumor increases in size. The guidelines have included observation as an option for this group of patients with resectable tumors. If progression occurs, they can be treated with surgery and/or radiation therapy and/or systemic therapy (see DESM-2, on page 957).

For symptomatic patients with large tumors causing morbidity, pain, or functional limitation, treatment choices (surgery and/or radiation therapy and/or systemic therapy) should be based on the location of the tumor and potential morbidity of the treatment. Postoperative treatment is dependent on the surgical margins (see DESM-2, on page 957). Treatment options include observation, radiation therapy, re-resection, or systemic therapy. In a recent report, sorafenib was active in patients (n = 26) with progressive disease on chemotherapy; it induced partial response in 25% of patients, and 70% experienced stable disease, with a median follow-up of 6 months.\(^3\) Based on these results, the panel has included sorafenib as an option for systemic therapy (see SARC-E, on page 958). Other systemic therapy agents recommended in the guidelines include nonsteroidal anti-inflammatory drugs (sulindac or celecoxib), hormonal or biologic agents (tamoxifen, toremifene, low-dose interferon, or imatinib), and chemotherapy (methotrexate and vinblastine, or doxorubicin-based regimens).

**References**

7. von Mehren M, Heinrich MC, Jonsuu H, et al. Follow-up results after 9 years (yrs) of the ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST) [abstract]. J Clin Oncol 2011;29(Suppl):Abstract 10016.


