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Gastrointestinal Stromal Tumors

Who Should Get Imatinib and for How Long?

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• Gastrointestinal stromal tumor • Imatinib • Sarcoma • Oncogenic kinase mutation

Key points

- Imatinib is the first-line therapy for patients with unresectable, recurrent, or metastatic gastrointestinal stromal tumor (GIST), except those with *PDGFRA* D842V mutations, which do not respond to imatinib.
- When there is imatinib resistance or intolerance in advanced disease, imatinib dose escalation, sunitinib, regorafenib, or clinical trials are indicated.
- Cytoreductive surgery may be considered for imatinib-sensitive or imatinib-stable advanced disease, although clinical trials are lacking.
- Adjuvant imatinib is indicated in patients who are deemed at intermediate to high risk for recurrence following resection of primary GIST.
- One year of adjuvant imatinib in intermediate-risk and high-risk patients decreases the risk of recurrence, but does not prolong overall survival. It is particularly beneficial in patients with *KIT* exon 11 deletions.
- Three years of adjuvant imatinib in high-risk patients decreases the risk of recurrence, but does not prolong disease-specific survival and may only be beneficial in patients with *KIT* exon 11 mutations.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common sarcoma, accounting for 18% of all sarcomas and 1% of all intestinal neoplasms [1]. The annual age-adjusted incidence in the United States is 7 cases per million, with a

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prevalence of 130 cases per million [2]. GISTs are hypothesized to arise from interstitial cells of Cajal, the intestinal pacemaker cells. GISTs can arise anywhere along the gastrointestinal tract but most commonly occur in the stomach and small intestine, and less frequently in the rectum, esophagus, or elsewhere in the abdominal cavity [3]. GISTs are aggressive tumors that have historically portended a poor prognosis. Approximately 50% of GISTs recur by 5 years after complete resection [4,5]. The tumor commonly spreads to the liver and peritoneum [2,3]. Historically, median survival in metastatic GIST was approximately 9 months, given its inherent resistance to chemotherapy and radiation [6].

In 1998, a groundbreaking discovery was made that GISTs arise as a result of oncogenic mutations in the *KIT* tyrosine kinase, and it was found subsequently that mutations in platelet-derived growth factor receptor α (*PDGFRA)* can also occur [7–9]. Over the past 15 years, much progress has been made in uncovering the kinase-driven biology of GIST and targeting the mutant oncoproteins. This research has translated into remarkable gains in clinical outcomes in GIST, and has stimulated considerable investigation into the role of kinase mutations and targeted agents in other solid tumors. GIST has become the most successful application of targeted therapy for the treatment of a solid cancer, with efficacy now demonstrated in both the adjuvant and metastatic settings.

ONCOGENIC KINASE MUTATIONS AND IMATINIB

It is now evident that 70% to 80% of GISTs harbor mutations in the *KIT* proto-oncogene and induce constitutive kinase activation, activate downstream signaling pathways that inhibit apoptosis, and stimulate cell proliferation. Mutations most commonly occur in the juxtamembrane domain in exon 11 that normally inhibits the kinase activation loop in the absence of ligand binding (Table 1). Deletions are the most common variant, with insertions and substitutions also seen (see Table 1). Extracellular (exons 8, 9) and kinase domain (exons 13, 17) mutations occur rarely [10]. About 8% of GISTs are driven by a *PDGFRA* mutation, which also then drives ligand-independent receptor activation. The landscape of mutations in *PDGFRA* is similar to that of *KIT*, with mutations found predominantly in the juxtamembranous domain, adenosine triphosphate–binding domain, or in the kinase activation loop. Ten percent to 15% of GISTs do not have a *KIT* or *PDGFRA* mutation and are termed wild-type (WT). Among these, 7% to 15% have now been found to harbor a *BRAF V600E* mutation, and 12% have a mutation in the succinate dehydrogenase (SDH) respiratory chain complex (see Table 1).

The initial discovery of *KIT* mutations in GIST by Hirota in 1998 fortuitously coincided with the clinical application of imatinib (Gleevec) for the treatment of the BCR-ABL kinase mutation that drives chronic myelogenous leukemia. Structural similarities between the BCR-ABL and KIT kinases prompted administration of imatinib to a patient with advanced GIST, resulting in a dramatic response [11]. This initial breakthrough triggered a wave of