

## Imatinib Efficacy in Gastrointestinal Stromal Tumours

a report by

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### Introduction

Gastrointestinal stromal tumours (GISTs) are morphologically spindle cell, epithelioid or occasionally pleomorphic mesenchymal tumours that usually arise from the gastrointestinal (GI) tract. They usually express the KIT protein and often harbour a mutation of a gene that encodes for a type III receptor tyrosine kinase (either KIT or platelet-derived growth factor receptor- $\alpha$  (PDGFR $\alpha$ )). Approximately 80% of GISTs have mutated KIT and 5% mutated PDGFR $\alpha$ .

KIT is transmembrane protein that functions as the receptor of the stem cell factor (SCF) and as a tyrosine kinase. Most KIT mutations occur in untreated GISTs in exon 11 that encodes the intracellular juxtamembrane part of the protein, and only rarely in exons that encode the intracellular kinase domain.

In imatinib-treated patients secondary mutations are frequent in exons encoding for the kinase domain (the ATP/imatinib binding pocket or the kinase activation loop).

### Diagnosis

GISTs vary in malignancy potential ranging from small, incidentally detected tumours with excellent outcome to aggressive sarcomas. The proportion of overtly malignant or high risk GISTs is 20–35% of all GISTs.<sup>1,2</sup> This suggests that the annual incidence of GISTs with a high malignancy potential is about five per one million.

Many small, asymptomatic GISTs may remain undetected, and the frequency of reported GISTs could change with time because of evolving diagnostic criteria and greater awareness of GIST.<sup>3</sup>

The KIT protein is detectable by immunohistochemical (IHC) assays, and the gene mutations can be detected by DNA sequencing. Other useful diagnostic features for GIST are negative immunostaining for desmin and absence of lymph node and lung metastases.

### Clinical Presentation

The most common symptom at presentation is bleeding.<sup>4</sup> Large GISTs often protrude from the site of origin and grow between the bowel loops and the abdominal organs, but they may also erode the GI tract lumen. Patients may also have various other symptoms, such as abdominal pain or discomfort, early satiety, bloating, obstructive jaundice, dysphagia, fever and anaemia-related symptoms, such as fatigue and palpitations,<sup>4</sup> or they may present with an abdominal tumour with no symptoms. Ten per cent to 25% of patients present with metastatic disease.<sup>1,5</sup>

GISTs can originate anywhere in the GI tract. The stomach (40–60%) and small intestine (30–40%) are the most common locations. The colon, rectum and oesophagus are other sites of origin. GISTs frequently give rise to numerous intra-abdominal metastases located on the peritoneal, omental, mesenteric and other serosal surfaces, and to liver metastases, but metastases outside the abdomen are rare. GISTs have a high tendency to seed. The intra-abdominal lesions probably result from tumour cell seeding into the abdominal cavity, whereas liver metastases probably result from haematogenous spread. GISTs range in size from a few millimetres to 35cm, with a median size of between 5cm and 8cm.<sup>1,6</sup> GISTs probably originate from the interstitial cells of Cajal or their precursors.<sup>7</sup> Interstitial cells of Cajal are the pacemaker cells of the GI tract controlling gut motility.

### Prognosis

Many GISTs have an uncertain malignancy potential. The most commonly used scheme to assess the risk of recurrence is the consensus approach, which is based on the primary tumour diameter and the mitotic count.<sup>8</sup>

According to Surveillance, Epidemiology, and End Results (SEER) registry data, the relative five-year survival rate for GIST patients diagnosed in the US between 1992 and 2000 was 45%.<sup>5</sup> The five-year

survival rate ranges from 50% to 65% after complete resection of localised primary tumour,<sup>9</sup> but 40–90% of surgical patients have a post-operative recurrence or metastasis. Median survival time of patients with metastatic or locally recurrent GIST was 10–20 months before the imatinib era.<sup>9</sup>

#### Treatment of GIST

Surgery is the standard treatment for non-metastatic GISTs. The tumour should be removed *en bloc* with its pseudocapsule to yield an adequate resection margin. The optimal width of the tumour-free margin has not been defined. *En bloc* resection is recommended whenever feasible in cases where nearby organs are involved.

The associated morbidity may be substantial when this requires total gastrectomy, pancreaticoduodenectomy or an abdominoperineal resection. In such cases, pre-operative treatment with imatinib may be considered, although at present there is no supporting evidence. Two clinical trials are currently under way to address the safety and efficacy of pre-operative imatinib.

#### Recurrent and Metastatic GIST

Imatinib mesylate is considered as the standard treatment of metastatic GIST. Approximately 65–70% of patients achieve a partial response, and another 15–20% have stabilised disease.<sup>10–12</sup>

also have longer median time to treatment failure compared with those with GIST with other types of mutations. Patients who have GIST with no detectable mutation of KIT or PDGFR $\alpha$  are less likely to respond to imatinib than those with an exon 11 mutation,<sup>13</sup> but up to 39% of these patients respond to imatinib.<sup>14</sup>

These results suggest that treatment with imatinib should be considered for virtually all patients who present with metastatic GIST regardless of the mutational status of the tumour.

A daily dose of imatinib (400–600mg) is considered as the standard starting dose. At present, continuous administration of imatinib is recommended in the treatment of advanced disease with no upper limit for treatment duration.

Adverse effects of imatinib therapy are usually mild to moderate. The most common adverse effects are oedema (usually periorbital), occasional muscle cramps in fingers and feet, diarrhoea, nausea/vomiting, fatigue and rash.

#### Imatinib-resistant GIST

The majority of patients with metastatic disease ultimately cease to respond to imatinib. The reasons for this include, secondary mutations at the ATP/imatinib binding pocket (exon 13 or exon 14) or in the activation loop (exon 17) of the KIT kinase that prohibit imatinib binding, but may also involve

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The median survival time of patients diagnosed with metastatic GIST and treated primarily with imatinib is not yet known; in a US-Finland randomised phase II study it was 4.8 years and had not yet been reached in the subgroup of patients with GIST with KIT exon 11 mutation.<sup>12</sup>

KIT and PDGFR $\alpha$  mutational status predicts for the likelihood of achieving response to imatinib. Patients with GIST harbouring an exon 11 KIT mutation have a partial response (PR) rate up to 85–90%, while those with an exon 9 KIT mutation have a PR rate of approximately 50%.

Patients who have GIST with a KIT exon 11 mutation

activation of other kinases and signalling routes, target gene amplification, increased imatinib metabolism or development of drug resistance.

Imatinib dose escalation beyond the 400mg daily dose benefits some patients who progress while receiving imatinib at this dose level, but the benefit is often not durable. Resistant lesions can occasionally be detected early by imaging. When other metastatic lesions continue to respond, surgical resection of the growing lesion may be considered.

Patients who progress in spite of imatinib dose escalation are candidates for a trial with other tyrosine kinase inhibitors. Sunitinib (SU11248) is an

inhibitor of KIT, PDGFR, fms-like tyrosine kinase-3 and vascular endothelial growth factor receptors (VEGFRs), and has been approved by the US Food and Drug Administration (FDA) for the treatment of GIST patients whose disease has progressed on imatinib or who are unable to tolerate treatment with imatinib.

As with other sarcomas, GISTs may be moderately sensitive to radiation therapy; selected patients may benefit from palliative irradiation of symptomatic metastases. Surgical removal of obstructing, bleeding or painful metastases may also be

worthwhile. Only a few (<5%) patients respond to conventional cancer chemotherapy and the response duration is generally short.

### Summary

Although administration of adjuvant imatinib appears attractive following removal of GIST with a risk for recurrence, this is of unproven value and considered experimental at time of writing. Adjuvant radiation therapy and adjuvant conventional chemotherapy have no proven therapeutic value, and are not recommended. ■

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