**CASE REPORT**

**Gastrointestinal stromal tumour treated with neoadjuvant imatinib**

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This report describes a case of unresectable primary gastrointestinal stromal tumour (GIST) treated with imatinib on a neoadjuvant basis, before subsequent successful surgical resection. After six months of imatinib, computed tomography and positron emission tomography imaging demonstrated a significant size reduction and complete metabolic response to treatment, rendering the tumour resectable. Mutational analysis showed an activating KIT mutation in exon 11. The pathological appearance of the resected tumour was heterogeneous with extensive necrosis, cystic and myxoid change, extensive hypocellularity, and patchy foci of residual viable tumour. The implications for this management option of radiological, pathological, and molecular assessment are discussed.

Gastrointestinal stromal tumours (GISTs) are rare, mesenchymal tumours of the gastrointestinal tract driven by activated KIT oncprotein, a type III receptor tyrosine kinase. Mutations in the KIT gene are the most common cause of activation. Imatinib mesylate (Glivec®/Gleevec®, formerly STI571; Novartis Pharma AG, Basel, Switzerland) is a selective tyrosine kinase inhibitor that inhibits the mutated KIT oncprotein. Imatinib has been used to treat patients with metastatic or unresectable GIST in phase I and II trials with considerable success. Phase II and III adjuvant imatinib trials and a single phase II neoadjuvant imatinib trial are under way. We report a case of unresectable primary GIST treated with imatinib on a neoadjuvant basis, before subsequent surgical resection.

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A 69 year old man presented with worsening abdominal swelling, dysphagia, and weight loss. Computed tomography (CT) and positron emission tomography (PET) scans revealed a 170 mm diameter metabolically active mass in the left upper abdominal quadrant (fig 1A, C). No metastases were evident. Needle core biopsy showed a tumour composed of interlacing fascicles of spindle cells with elongated nuclei and weakly eosinophilic cytoplasm. Immunohistochemistry revealed membranous CD117 (KIT) positivity, confirming a diagnosis of GIST. Automated sequencing of KIT exon 11 identified a GAA→TCC trinucleotide substitution at base position 1671–1673, resulting in a WK→CP double amino acid change at residues 557 and 558.

The tumour was considered unresectable and treatment was begun with imatinib 400 mg/day. A rapid clinical response followed. Restaging scans were performed after three and six months. CT revealed a reduction in tumour diameter of approximately 50% after six months (fig 1B). Both PET scans showed a total loss of [18F] fluorodeoxyglucose uptake, indicating a sustained complete metabolic response (fig 1D). At this stage, the tumour was considered resectable. At laparotomy, the tumour was soft but well encapsulated, and arose from a narrow base in the anterior wall of the stomach. Complete surgical resection without tumour rupture was performed successfully with a partial gastrectomy.

Pathological examination of the resection specimen revealed a lobulated, pale grey tumour measuring 120 mm in maximum diameter (fig 2A). The tumour was heterogeneous with extensive gelatinous change, cystic degeneration, a large central necrotic area, and nodules of more solid, fleshy tissue. Microscopy confirmed widespread myxoid degeneration with cystic change, necrosis, and hypocellularity (fig 2B, C). Nodules of residual viable CD117 positive tumour cells made up approximately 10% of the overall tumour volume (fig 2D). Mutational analysis repeated using DNA extracted from residual tumour tissue showed the same KIT exon 11 mutation, but no acquired KIT mutations, in exons 11 and 17.

The patient made a rapid recovery postoperatively. Follow up CT and PET scans at four weeks confirmed no residual disease and imatinib treatment was stopped. The patient will continue with surveillance imaging at three monthly intervals initially, with reintroduction of imatinib should disease recur.

**DISCUSSION**

Reports of GIST resection after treatment with imatinib are limited. One series describes 17 patients with initially unresectable GISTs who underwent tumour resection after a median of 10 months of treatment with imatinib. Thirteen patients had a partial (11) or complete (two) pathological response, based on evaluation of residual viable tumour cells. Hohenberger et al recently reported 18 patients with GIST treated surgically after imatinib pretreatment. Patients with evidence of a partial response at the time of surgery had a much better outcome than those with progressive disease. Two other reports describe the successful use of neoadjuvant imatinib in one and two cases, with complete resection of tumour after partial response to the drug. Pathological tumour changes described after treatment with imatinib were similar to those seen in our case, namely tumour necrosis, hypocellularity, myxoid change, and sclerosis.

Recent series looking at the prognostic value of KIT mutations in GISTs treated with imatinib alone have reported
Figure 1  Computed tomography (CT) and positron emission tomography (PET) imaging response to imatinib in a patient with advanced, gastric gastrointestinal stromal tumour: (A, C) before imatinib treatment, (B, D) after six months of imatinib 400 mg/day. Note the approximately 50% reduction in size on CT imaging (B) and total loss of [18F] fluorodeoxyglucose uptake on PET scan (D), indicating a complete metabolic response.

Figure 2  (A) Gastrointestinal stromal tumour (GIST) resection specimen after treatment with imatinib, macroscopically showing normal gastric mucosa (top left) and underlying heterogeneous tumour with extensive gelatinous change, a central necrotic area, and nodules of solid pale tissue containing residual viable tumour. (B–D) Representative GIST tumour sections. (B) Low power view showing cystic change and adjacent residual tumour (right). (C) Myxoid degeneration and hypocellularity. (D) Residual viable spindle shaped tumour cells, identical to pretreatment biopsy (haematoxylin and eosin stain; original magnification, ×100–200). (Inset) Diffuse membranous positivity for CD117 (KIT) in tumour cells (CD117 immunohistochemistry; original magnification, ×200).
an increased likelihood of partial response and longer median survival times in GISTs harbouring exon 11 mutations compared with all others (non-exon 11 mutations and wild type).11-13 Most KIT exon 11 mutations in GISTs are in frame deletions involving the region between residues 553 and 561, but missense mutations, including those of several adjacent bases causing double amino acid substitutions, have been reported, mainly at the 557–558 hotspot.11 In the neoadjuvant setting, preoperative genotyping may give an indication of the likely response to imatinib and could be used in developing a treatment plan. However, it has been shown that, after a good initial response to treatment, exon 11 mutated GISTs treated with imatinib may develop disease progression, usually because of the acquisition of secondary KIT mutations, conferring drug resistance.12 Hence, the timing of surgical intervention after neoadjuvant imatinib is important. In most GISTs that respond to imatinib, the initial response lasts at least 12 months before progression occurs. Surgical intervention should be targeted towards this window, aiming at the time of maximal response but before progression occurs. Close monitoring with CT and PET scanning during this period is important. No secondary KIT mutation was found in our case in the residual tumour tissue unresponsive to imatinib treatment.

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Often, the assessment of resectability on the basis of CT scanning with or without laparoscopy is imperfect. In cases of doubtful or marginal resectability, preoperative imatinib may render a tumour clearly resectable. Tumour rupture is known to be associated with a high risk of disseminated intraperitoneal recurrence. A major reduction in tumour size may make rupture less likely, although the treatment induced necrosis and myxoid changes may increase this risk.

Our case of partial response to imatinib treatment and successful resection of a previously unresectable primary GIST supports the use of imatinib in the neoadjuvant setting. Consideration should be given to preoperative KIT mutation analysis if available. The outcome of prospective randomised trials evaluating this management strategy is awaited.

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