

The role of surgery in an imatinib-resistant GIST liver secondary

E Loots, FCS (SA), Cert Gastro (SA) Surg

Department of General Surgery, Inkosi Albert Luthuli Central Hospital; and Department of General Surgery, University of KwaZulu-Natal, Durban, South Africa

Corresponding author: E Loots (emiloots@hotmail.com)

This is a case report describing the management of an imatinib-resistant liver secondary as a result of an exon 13 mutation. The gastric primary was completely excised 3 years prior and proven to contain an exon 11 mutation. Resective liver surgery was undertaken after the patient developed imatinib resistance and he has been disease-free for 19 months. The application of surgery in the context of other treatment options is discussed.

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Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumour of the gastrointestinal tract. The expression of protein tyrosine kinase KIT (CD117) has changed the diagnostic landscape of this condition. Targeted therapies with tyrosine kinase inhibitors (TKI) have led to an improvement in median survival rates of up to 5 years, mostly accomplished with imatinib, which is considered as the standard induction therapy.^[1] Complete or partial response can be achieved in up to 90% of cases with imatinib.^[2] However, germline mutations affect the likelihood of response to this agent. A lack of KIT or platelet-derived growth factor alpha (PDGRF α) implies a poor response to imatinib.^[3] Secondary resistance after initial response or stable disease may develop in up to 50% of treated patients as a result of secondary kinase mutations.^[3] The mechanism of exon mutations is still poorly understood. The role of surgery for secondary resistance is limited and controversial. This report describes the natural history and treatment of a patient developing secondary resistance to imatinib as a result of a secondary exon 13 mutation.

Case report

A 71-year-old male presented 5 years ago with a haemodynamically insignificant upper gastrointestinal bleed. Chronic health problems included diabetes mellitus, hypertension and stable ischaemic heart disease. An exophytic lesion on the greater curve of the stomach was identified and biopsied at endoscopy. A positive KIT test confirmed a gastrointestinal stromal tumour (GIST). Computed tomography (CT) combined 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan excluded distant metastases. A laparotomy was performed with a wedge resection of an 8 × 7 cm lesion of the greater curve of the stomach. The immunohistochemistry identified CD117 and CD34 with an exon 11 deletion mutation and a high mitotic index.

Surveillance with FDG-PET was performed at 3-monthly intervals and a metastatic lesion of the left lobe of the liver was diagnosed at 1-year follow-up. Imatinib was commenced and FDG-PET activity

decreased significantly. The patient declined resective surgery of the liver lesion and was followed up with 3 - 6 monthly FDG-PET scans. There was no further increase in the size or activity of the lesion over the next 4 years until a sudden increase in FDG-PET activity of the involved lesion was noted. Second-line treatment with sunitinib was unavailable at our institution. A left liver lobectomy was performed achieving clear resection margins with an uneventful postoperative course. Immunohistochemistry of the liver lesion demonstrated exon 11 and 13 mutations with a high mitotic index. An exon 13 mutation was retrospectively excluded from the initial gastrectomy specimen.

Discussion

The case describes the natural history of a patient with a GIST of the stomach developing secondary resistance to imatinib in a liver metastasis. GIST tumours are most frequently observed in the stomach followed by the small bowel, colorectum, oesophagus and mesentery.^[2] Metastasis to the abdominal serosal surfaces and liver are the most frequent sites for spread, whereas lung and lymph node spread occur in less than 5% of cases.^[2]

Mutated KIT is expressed in about 80% of GISTs with a further 5% expressing mutated platelet-derived growth factor alpha (PDGRF α) mutations. The remainder (10 - 15%) non-KIT or/and non-PDGRF α are known as wild type, which is poorly understood. Both wild type and PDGRF α are associated with poor treatment response to imatinib. KIT gene mutation to exon 11 occurs in 70% of cases and is responsive to treatment with imatinib (400 mg/day). Up to 95% of these cases may display either an arrest in tumour growth or regression. However, in 15% of cases an exon 9 mutation exists, which has a less favourable response to treatment requiring a higher dosage of imatinib (600 - 800mg/day). Other primary mutations such as exon 13 and 17 are uncommon and are generally resistant to imatinib, therefore requiring second-line tyrosine kinase inhibitors (TKI) therapy with sunitinib.^[3]

Complete local excision as applied in the index case provides the only potential for cure when sunitinib is unavailable. Pre-operative

treatment with imatinib is advised where multivisceral resection or complete organ removal is likely or where complete resection of a large tumour may be hazardous. The optimal duration has not been established and recommendations vary from 3 to 12 months.^[1]

Metastatic GIST warrants definitive treatment with imatinib. Planned metastatectomy is controversial and has not been proven beneficial in prospective trials. However, surgical resection of metastatic disease may prevent the development of secondary resistance and should be considered. Isolated liver lesions in stable or responsive disease should only be considered for resection or ablation in a multidisciplinary setting or as part of a clinical trial.^[2]

Adjuvant imatinib therapy for a 3-year period improves recurrence-free and overall survival rates in high-risk cases. The risk estimation is based on tumour size, location in the gastrointestinal tract, mitotic rate (>10/50 high-power fields) and whether intra-operative tumour spillage occurred at the time of surgery. Guidelines for adjuvant therapy in the intermediate- and low-risk groups are lacking and not currently advised.^[4]

The development of treatment resistance following initial susceptibility to imatinib equates to secondary resistance. This is retrospectively confirmed by typing the initial tumour specimen to exclude the new mutation as demonstrated in the case. It is clear from the literature that some cases labelled secondary mutations may have been a primary mutation from the outset. The most common sequence is a primary mutation on exon 11 followed by a secondary mutation on exon 17.^[3]

CT scan with contrast enhancement is widely recommended for radiological follow-up in GIST patients. The response to evaluation criteria in solid tumours is commonly applied to monitor radiological response to treatment. Secondary resistance may be suspected if an increase in size or activity is noted in a previously responsive tumour or stable disease. CT scan with contrast enhancement may accurately diagnose an increase in

size but cannot identify increased metabolic activity. FDG-PET CT scan resolves this problem provided it was used as a baseline investigation and repeated after introduction of treatment, as demonstrated in the case report.^[6]

Secondary mutations require either dose escalation of imatinib or second-line TKI therapy with sunitinib.^[4] Surgery has a limited role in this setting and is not advocated by some because the tumour-free period is not affected.^[5] However, a single lesion with proven PET activity in the presence of multiple inactive lesions should be removed since other lesions may remain sensitive to first-line treatment. Few patients will benefit from surgery in secondary resistance and careful patient selection is essential.^[2]

In conclusion, a single resectable lesion with no possibility of second-line therapy in a resource-constrained environment is a necessary therapeutic option. Exon typing of a GIST holds clues in deciding on future second-line TKIs or surgery as an option of management of secondary lesions.

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