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Gastro-intestinal stromal tumours are uncommon malignancies of the gastro-intestinal tract, accounting for only 0.2% of all gastro-intestinal malignancies, but are the most common of abdominal sarcomas. Classically, they have been considered amenable only to early stage surgical intervention. Recent advances in targeted cancer therapies have led to the development of effective non-surgical treatment options. This article discusses the epidemiology and pathophysiology of, as well as treatment options available for, this uncommon disease.

Introduction

Gastro-intestinal stromal tumours (GISTs) are rare tumours of the gastro-intestinal (GI) tract, mesentery, and omentum. Nonetheless, malignant GIST is the most common sarcoma of the GI tract and accounts for 5% of all sarcomas.¹ The estimated annual incidence is 10 to 20 cases per million, of which 20 to 30% are malignant.² There is long-standing confusion and controversy regarding their origin, differentiation, nomenclature, diagnosis, and prognosis. For many years, spindle cell neoplasms of the GI tract were classified as leiomyomas or leiomyosarcomas, whereas epithelioid stromal tumours were labelled as leiomyomas, leiomyoblastomas, or epithelioid leiomyosarcomas. Immunohistochemistry techniques later proved that most of these tumours lacked evidence of smooth muscle differentiation. It has been proposed recently that most stromal tumours arise from mesenchymal stem cells that differentiate toward the interstitial cells of Cajal.

Histopathology and immunochemistry

There are two histological categories of GIST: spindle cell (70%) and epithelioid (30%) types. Only in rare cases are both patterns present. Cell types appear to have limited prognostic relevance but the mitotic threshold for malignancy is reportedly lower in epithelioid tumours. The electron microscopic features of GIST are notably heterogeneous and can show either smooth muscle fibres, neuronal differentiation, or be quite undifferentiated.

Gastro-intestinal stromal tumours are consistently immunoreactive for c-KIT receptor tyrosine kinase (CD117 antigen) in most, if not all, cases.³ The immunohistochemical profile of a typical GIST is compared to that of other tumours in Table 1.

Clinical features

Gastro-intestinal stromal tumours are most commonly found in the stomach (40-70%), but can occur in all other parts of the GI tract. About 20 to 40% of GISTs arise from the small intestine, and 5 to 15% from the colon and rectum.¹ They have also been found in the oesophagus (<5%), omentum (<5%), mesentery, and retroperitoneum. They typically grow endophytically, parallel to the bowel lumen, commonly with overlying mucosal necrosis and ulceration. They also vary in size, from a few mm to 40 cm in diameter. Large, high-grade GIST lesions can be necrotic and haemorrhagic and show more mucosal ulceration than small GISTs. Many GISTs are well defined by a thin pseudocapsule. Over 95% of patients present with a solitary primary tumour, and in 10 to 40% of these cases the tumours directly invade neighbouring organs.

Small GISTs are most often discovered incidentally during laparotomy, endoscopy, or imaging for other reasons. Gastro-intestinal stromal tumours usually present as a vague abdominal mass, a feeling of abdominal fullness, or with secondary symptoms from tumour bleeding and an associated anaemia. Other presenting symptoms include altered bowel functions, bowel obstruction or perforation, dysphagia, and fever.

Most recurrences are solely intra-abdominal. Macroscopic extra-abdominal metastases are uncommon, even in advanced disease, and they rarely occur in the absence of abdominal

Key words

Epidemiology; Gastrointestinal stromal tumors; Gastrointestinal tract; Pathophysiology

Hong Kong Med J 2007;13:61-5

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腸管基質瘤：對現時療法的討論

腸管基質瘤是罕見的腸管道惡性瘤，佔所有腸管道惡性瘤的0.2%，但卻是腹部肉瘤最常見的一種。過往這疾病只能在病發初期以創傷手術治療才有治愈機會，但近來針對癌症療法的改進，帶來非創傷手術治療方法的發展。本文討論此罕見疾病的流行病學和病理生理學情況，以及可選擇的治療方法。

TABLE 1. Immunohistochemical profiles of gastro-intestinal stromal tumours (GIST) compared to other tumours

	KIT	CD34	SMA	Desmin	S-100
GIST	+	60-70%	30-40%	Rare	5%
Smooth muscle tumour	-	10-15%	+	+	Rare
Schwannoma	-	+	-	-	+
Fibromatosis	Disputed	Rare	+	Rare cells	-

recurrence. Approximately 40 to 80% of GISTs recur despite histopathologically confirmed complete resection. The most common sites for metastases are the peritoneum and liver; lymph node metastases are rare.

Clinical diagnosis

The clinical diagnosis of GIST requires a high index of suspicion. On computed tomographic scan, the diagnosis of GIST should be considered in the presence of a circumscribed mass that is associated closely with the stomach or intestine, especially if there is internal tumour necrosis or haemorrhage. Gastro-intestinal stromal tumours tend to be avid in positron emission tomography with ¹⁸fluorodeoxyglucose. However, due to the rarity of the tumour, most GISTs are not diagnosed until laparotomy and/or pathologic examinations are performed. Gastro-intestinal stromal tumours are staged by cross-sectional imaging of the abdomen and pelvis, preferably with computed tomography using both intravenous and oral contrast media. A chest X-ray is sufficient for thoracic evaluation, as it rarely metastasises to the lungs. Bone scans should be reserved for patients with specific symptoms.

Surgical management

Standard therapy for a primary GIST in the absence of metastasis is complete surgical resection, as this provides the best chance of cure. The Memorial Sloan-Kettering Cancer Center group⁴ considers a preoperative biopsy unnecessary and unwarranted if the patient is outside of a clinical trial. The main reason for avoiding a biopsy is that GISTs tend to be fragile and friable. A biopsy may

induce intraperitoneal bleeding, rupture, and tumour dissemination, all of which are associated with a poor outcome.⁵ Furthermore, large tumours may have extensive intra-tumour haemorrhage and necrosis; consequently, a biopsy may not yield diagnostic information.

During resection of a GIST, meticulous surgical technique is required. The tumour capsule tears easily and this may lead to bleeding. The GIST tends to protrude from the tissue of origin and displace surrounding structures, unlike many other intra-abdominal malignancies (eg adenocarcinoma), so only a wedge resection of the site of origin is necessary. Nevertheless, the surgeon should attempt to obtain microscopically negative margins. Lymphadenectomy is not usually indicated in patients with GISTs because lymph node metastases are so rare.

The literature concerning surgical resection in patients with primary GIST has several limitations. Most reports discuss few patients because the disease is uncommon. Essentially, all studies are retrospective and span a long period (eg 20-30 years). Most results are also confounded by the inclusion of patients with other GI sarcomas because of the previous inconsistency in the definition (Table 2^{1,5-8}).

In terms of prognosis, tumour size, mitotic activity, and anatomical location have all been described as predictive factors. In the Memorial Sloan-Kettering Cancer Center series, tumour size was an independent prognostic factor for survival on a multivariate analysis. Patients with tumours larger than 10 cm had a relative risk of 2.5 (confidence interval, 1.2-5.5) and only a 20% actuarial 5-year survival rate. The site of origin also has predictive value. Oesophageal GISTs are often diagnosed late and are associated with poor outcomes. People with gastric GISTs typically do better than those with GIST originating in the small bowel. The right description for a GIST—as benign or malignant—has

TABLE 2. Published series of surgical resection of gastro-intestinal stromal tumours^{1,5-8}

Author (Institution)*	Years	No. of patients	No. of complete resection	5-year survival (%)
Akwari et al ⁶ (Mayo Clinic)	1950-74	108	52	50
Shiu et al ⁷ (MSKCC)	1949-73	38	20	65
McGrath et al ⁸ (MCV)	1951-84	51	30	63
Ng et al ⁵ (MDACC)	1957-87	191	99	48
DeMatteo et al ¹ (MSKCC)	1982-98	200	80	54

* MSKCC denotes Memorial Sloan-Kettering Cancer Center, MCV Medical College of Virginia, and MDACC MD Anderson Cancer Center

TABLE 3. Criteria used for stratification between low- and high-risk groups

Low-risk group	High-risk group
Tumour size <5 cm, mitotic rate of <2/10 high power fields; OR EITHER size of >5 cm OR mitotic rate of >2/10 high power fields AND proliferation index of <10%	Tumour size >5 cm AND mitotic rate of >2/10 high power fields; OR EITHER size of <5 cm OR mitotic rate of <2/10 high power fields AND proliferation index of >10%

been an issue of intense controversy. Most pathologists avoid using the term benign and instead classify GIST as having a low or high risk of being malignant. In a recent retrospective analysis, Langer et al⁹ determined that tumour size of larger than 5 cm, mitotic count of more than 2, proliferation index of higher than 10% (Table 3) were all significantly associated with a shorter recurrence-free survival rate ($P=0.02$, $P=0.001$, and $P=0.02$ respectively).

Conventional chemotherapy

Gastro-intestinal stromal tumours are widely considered refractory to conventional chemotherapy. Consequently, the standard management after complete resection of a primary GIST has been observed. Zalupski et al¹⁰ showed that only 7% of patients responded to a combination of doxorubicin and dacarbazine, compared with a 22% response for uterine leiomyosarcomas and a 21% response in leiomyosarcomas in other sites.

Radiotherapy

The impact of radiotherapy on the outcome of GIST is unknown. It is not a standard postoperative therapy for GIST and should be reserved for limited, palliative

settings.

STI-571 (imatinib mesylate) in the treatment of gastro-intestinal stromal tumours

Recent research and clinical studies have focused on the use of STI-571 (imatinib mesylate) as treatment for metastatic GISTs. STI-571 is a competitive inhibitor of some tyrosine kinases, including intra-cellular kinases ABL and BCR-ABL fusion protein, c-KIT, and platelet-derived growth factor receptors (Fig 1). STI-571 was first approved by the United States Food and Drug Administration in May 2001 for the treatment of chronic myeloid leukaemia (CML) in which it specifically inhibits the BCR-ABL fusion protein. STI-571 was shown to induce complete responses in more than 90% of patients in the chronic phase of CML.

As in CML, the pathogenesis of GIST seems to depend primarily on aberrant tyrosine kinase activity. The proto-oncogene c-KIT, with its ligand being a stem-cell factor, encodes a transmembrane tyrosine kinase receptor located on the long arm of chromosome 4 (4q11-q12). This proto-oncogene has a role in the development of normal haematopoiesis as well as in the migration of germ cells and is also expressed in normal human mast cells, immature myeloid cells, melanocytes, epithelial breast cells, and the interstitial cells of Cajal.

In approximately 60% of GISTs, there are mutations in c-KIT in the juxtamembrane domain, such as in-frame deletions (3 to 18 bp) and point mutations in exon 11. The reported rate of mutation ranges from 21 to 88%. Mutations in exon 13 and exon 9 have also been found. The mutations cause the receptor to be activated constitutively without its ligand (Fig 2). Gastro-intestinal stromal tumours with mutant c-KIT are more likely to be high-grade tumours, characterised by more frequent recurrences and a higher mortality rate than GISTs with normal c-KIT.

Imatinib in metastatic gastro-intestinal stromal tumours

The first patient with metastatic GIST treated by STI-571 was a patient who had failed a variety of therapies. After treatment with STI-571, started in February 2000, the tumour underwent myxoid degeneration, confirmed by histological analysis. These initial observations prompted further clinical trials, including the US-Finland Study, headed by Demetri et al¹¹ at the Dana-Farber Cancer Institute. They reported a partial response rate of 54% among 147 patients with inoperable or metastatic GIST using a daily dose of 400 to 600 mg. Similar results were found in the European Organization for Research and Treatment of Cancer trial¹² (Table 4).

The US-Finland Study Group¹¹ also assessed the toxicity and safety of STI-571 and it was found to be

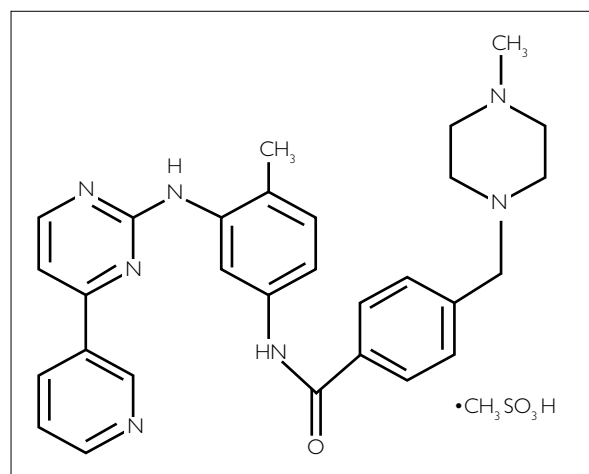


FIG 1. Chemical structure of imatinib mesylate (STI-571)

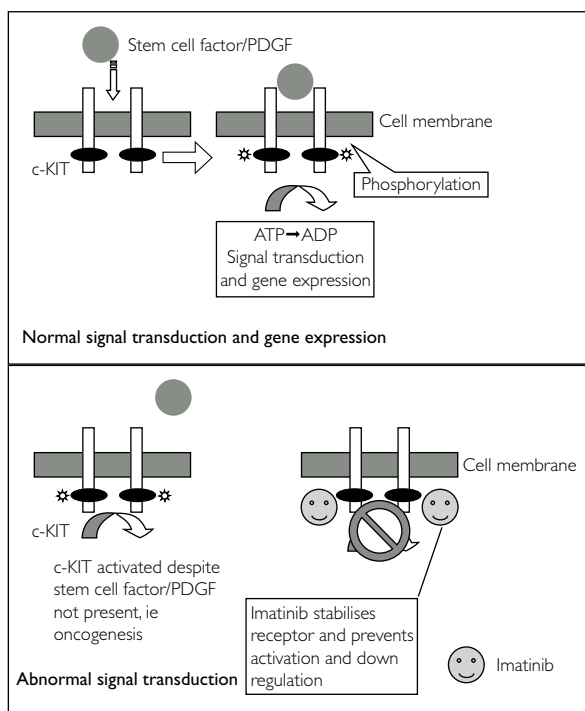


FIG 2. Diagram showing receptor activated constitutively without a ligand. Imatinib mesylate (STI-571) stabilises the receptor and prevents activation

PDGF denotes platelet-derived growth factor

TABLE 4. Results of STI-571 in patients with metastatic gastro-intestinal stromal tumours (GIST)

Variable	US-Finland GIST Study Group ¹¹ (n=147)*	European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group ¹² (n=36) [†]
Partial response (%)	54	69 (partial and minor)
Stable disease (%)	28	19
Progression (%)	14	11
Could not be evaluated (%)	4	1

* Dose ranged from 400 to 600 mg daily

[†] Dose ranged from 400 to 1000 mg daily

dramatically improved the quality of life and survival of patients with advanced disease; however, it is apparent that it does not cure the vast majority of patients. Both primary and secondary imatinib resistance has been described. Primary resistance is defined as patients who do not achieve stable disease or who progress within 6 months of an initial objective response. Molecular analysis has shown that the majority of these tumours have a KIT exon 9 mutation,¹⁴ whilst some have no detectable kinase mutations (wild-type tumours).

Patients with secondary resistance develop one or more sites of progression after 6 months of measurable benefit. These have been associated with secondary kinase mutations found in KIT that interfere with imatinib activity. The emergence of these secondary mutations suggests that in GISTs, imatinib acts as a cytostatic rather than a cytocidal agent.

There remains no consensus on the management of imatinib resistance. Patients should be evaluated for possible surgical resection and/or radiofrequency ablation of resistant tumours. Alternatively, a number of newer inhibitors, such as SU11248, have also shown promise in early and phase III clinical trials.¹⁵

The future: imatinib as neoadjuvant treatment?

Contemporary management of GIST appears to be moving toward the combined use of systemic tyrosine kinase inhibitor therapy and surgical resection to optimise clinical outcomes. The introduction of imatinib in the neoadjuvant setting to 'debulk' primary and/or metastatic disease prior to surgery may render previously inoperable patients suitable for operation. Reducing the area and size of resection needed, may also allow surgeons to perform a less morbid procedure.

A multicentre phase II trial (RTOG S-0132¹⁶) is currently being conducted by the Radiation Therapy Oncology Group to investigate the efficacy of imatinib in

generally acceptable. There were a few patients (around 5%) who developed bleeding as a result of rapid tumour necrosis induced by the agent. Common side-effects were diarrhoea, periorbital oedema, and fatigue. Others included transient nausea, muscle cramps, headaches, dermatitis, anaemia, and neutropenia. Most adverse effects resolve within days to weeks after cessation of treatment, and most patients can continue at a lower dose.

The data mentioned above, coupled with experience with the use of imatinib in patients with CML, led the United States Food and Drug Administration to approve the use of imatinib mesylate for the treatment of malignant metastatic and/or unresectable GISTs on 1 February 2001. The recommended dose is 400 or 600 mg daily.

There remains no consensus on the duration of imatinib treatment in advanced GIST. Imatinib interruption after 1 year is associated with a high risk of relapse, even for patients in complete remission.¹³ Although most patients responded to imatinib reintroduction, the drug should not be discontinued outside of a clinical trial. Imatinib should therefore continue to be given until there are strong reasons for stopping, such as disease progression, patient intolerance, or refusal.

Management of imatinib-resistant gastro-intestinal stromal tumours

Recent data have shown that the use of imatinib has

the neoadjuvant setting. Suitable patients are pretreated with 8 to 10 weeks of imatinib prior to surgery. Imatinib is continued for 24 months postoperatively if the tumour is deemed responsive. We eagerly await the results of this clinical trial.

Conclusion

Despite being a rare and formerly poorly defined pathologic entity, the recent innovations and advances in GIST treatment and management have made it an important condition in oncology. Use of imatinib treatment for GIST has become the paradigm of oncogene

treatment for solid tumours. As a consequence, the treatment of GIST has evolved rapidly, with dramatic changes in clinical practice.

At present, surgery remains the only known curative treatment for localised GIST. However, with the advent of kinase inhibitors such as imatinib, patients with advanced GIST can also benefit from disease control and remission. By combining treatment modalities and the expertise of both surgeons and medical oncologists, the future research direction is one incorporating a multi-disciplinary approach. Further insight into issues of dosage, treatment duration and the selection, timing and monitoring of therapeutic interventions for GISTs are needed.

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