

# Gastrointestinal stromal tumours: Etiology, pathology and clinical management

Martin E Blackstein MD PhD FRCPC FACP<sup>1</sup>, Pierre Dubé MD FRCSC<sup>2</sup>, Jonathan A Fletcher MD<sup>3</sup>, Oliver R Keller MD FRCPC<sup>4</sup>, Margaret Knowling MD FRCPC<sup>5</sup>, Richard Létourneau MD FRCSC<sup>6</sup>, Donald Morris MD PhD FRCPC<sup>7</sup>, Robert Riddell MD FRCPC<sup>1</sup>, Stewart Rorke MD FRCPC<sup>8</sup>, Carol J Swallow MD PhD FRCSC FACS<sup>1</sup>, on behalf of the Canadian Advisory Committee on GIST\*

## \*Canadian Advisory Committee on Gastrointestinal Stromal Tumours

Martin E Blackstein MD PhD FRCPC FACP Chair<sup>1</sup>, Mark S Dorreen MD FRCPC<sup>9</sup>, Pierre Dubé MD FRCSC<sup>2</sup>, Jonathan A Fletcher MD<sup>3</sup>, Oliver R Keller MD FRCPC<sup>4</sup>, Margaret Knowling MD FRCPC<sup>5</sup>, Richard Létourneau MD FRCSC<sup>6</sup>, Donald Morris MD PhD FRCPC<sup>7</sup>, Robert Riddell MD FRCPC<sup>1</sup>, Stewart Rorke MD FRCPC<sup>8</sup>, Denis Soulières MD FRCPS<sup>6</sup>, Carol J Swallow MD PhD FRCSC FACS<sup>1</sup>, Ralph Wong MD FRCPS<sup>10</sup>

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Investigation of the regulation of cell growth, differentiation and death by signalling pathways has led to a greater understanding of how alterations in these pathways play a critical role in the development of some cancers, and has opened new opportunities for their treatment. In the present review, results with the prototype drug of

this class, imatinib (Gleevec, Glivec [formerly STI571]; Novartis, Switzerland), in metastatic gastrointestinal stromal tumours are presented. The present review originated from a conference of the authors held in Montreal, Quebec in June 2003, under the sponsorship of Novartis.

**Key Words:** *Gastrointestinal stromal tumour (GIST); Imatinib; Targeted molecular therapy*

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal (GI) tract; nevertheless, they account for no more than 1% of all GI tumours (1). GISTs occur most frequently in patients over the age of 40 years and equally in both sexes (2). The most common primary sites are the stomach (60% to 70% of cases) and small intestine (30%), but GISTs may also develop in the colon or rectum and esophagus (2,3).

Little is known about the pathogenesis or natural history of GISTs. While GISTs were generally classified as mesenchymal or smooth muscle tumours, some clearly have evidence of autonomic neural differentiation and were called gastrointestinal autonomic nerve tumours or plexosarcomas. However, these tumours are also CD117-immunoreactive, so it is no longer necessary to carry out electron microscopy for evidence of neural differentiation. GISTs are now considered to be mesenchymal gut neoplasms that originate from the interstitial cells of Cajal (ICC), which act as pacemaker cells to coordinate peristalsis throughout the GI tract. Estimates of the five-year survival for GISTs range widely but are typically 35% to 65% (4).

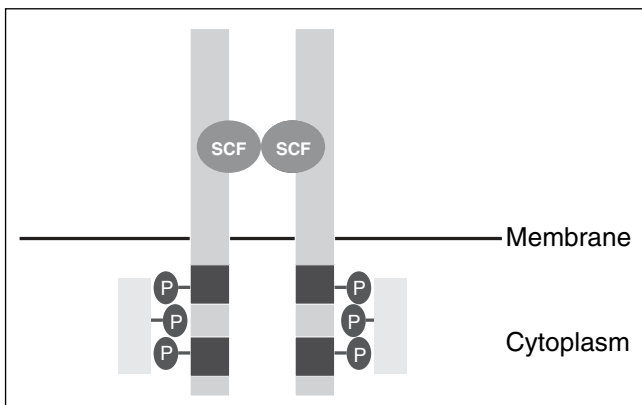
Several factors, such as tumour size, mitotic index and tumour location, have prognostic value (4-6), but their effects on clinical course have not been fully determined.

The unique histological, immunophenotypic and genetic features of GISTs distinguish them from other, more typical, esophageal tumours and leiomyomas. Of particular importance is their immunohistochemical profile. Between 84% and 94% of GISTs are positive for c-KIT protein (CD117) and CD34 (7-9). A majority of GISTs have c-KIT-activating mutations, and the type and location of these mutations have proved to be important predictors of therapeutic response and disease-free survival (10).

GISTs are resistant to chemotherapy and radiotherapy, and unresectable or metastatic tumours were considered to be untreatable as recently as five years ago. More recently, however, improved understanding of the molecular bases underlying GIST growth and proliferation and treatment with novel agents such as the tyrosine kinase (TK) inhibitor, imatinib, have resulted in significant improvements in the clinical response and quality of life for patients with GIST.

<sup>1</sup>Mount Sinai Hospital, Toronto, Ontario; <sup>2</sup>Centre Hospitalier Maisonneuve-Rosemont, Montreal, Quebec; <sup>3</sup>Brigham and Women's Hospital, Boston, Massachusetts, USA; <sup>4</sup>Ottawa Regional Cancer Centre, Ottawa, Ontario; <sup>5</sup>British Columbia Cancer Agency – Vancouver Cancer Clinic, Vancouver, British Columbia; <sup>6</sup>Centre Hospitalier de l'Université de Montréal, Montreal, Quebec; <sup>7</sup>Tom Baker Cancer Centre, Calgary, Alberta; <sup>8</sup>Dr H Bliss Murphy Cancer Centre, St John's, Newfoundland; <sup>9</sup>Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; <sup>10</sup>St Boniface General Hospital, Winnipeg, Manitoba

Correspondence: Dr Martin E Blackstein, 600 University Avenue, Suite 1222, Mount Sinai Hospital, Toronto, Ontario M5G 1X5. Telephone 416-586-5371, fax 416-586-5165, e-mail martin.blackstein@utoronto.ca



**Figure 1)** Ligand-dependent activation of wild-type KIT. P Phosphate; SCF Stem cell factor

The present review summarizes the current data on the pathology and molecular genetics of GISTs, and presents the current clinical consensus on the optimal management approach.

#### NATURAL HISTORY AND PATHOLOGY OF GIST

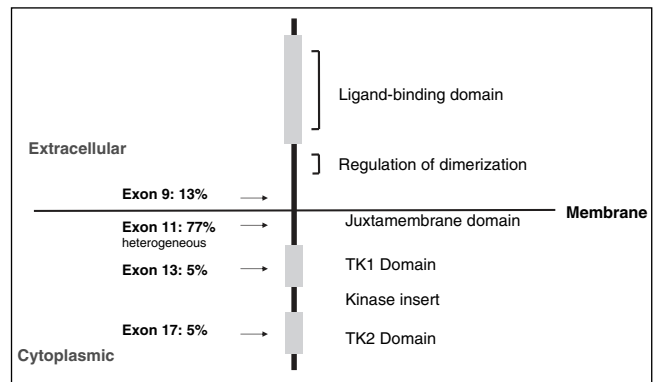
GISTs have morphological and immunophenotypic similarities to ICCs and appear to originate from cells that differentiate toward an ICC phenotype (11,12). GISTs most commonly display spindle cell histology, but epithelioid and mixed cell-type patterns have also been described (2).

It has been established that the c-KIT (CD117) TK receptor and its interaction with its ligand stem cell factor are required for melanogenesis, hematopoiesis, gametogenesis, ICC development, and the growth and differentiation of mast cells. In the normal physiology of c-KIT, there is an extracellular component that binds to the stem cell factor and enables it to interact with another receptor (Figure 1). The change in structure activates the intracellular kinase domains, which cross-phosphorylate critical tyrosine residues, thus serving as binding sites for other proteins which in turn become phosphorylated. This process constitutes a signalling pathway that leads to nuclear events that drive cell proliferation and survival.

#### c-KIT mutation

The clinical significance of c-KIT gain-of-function mutations in GIST was first reported by Hirota et al (7) in a study of 58 mesenchymal tumours, of which 49 were diagnosed as GISTs. Immunohistochemical analysis demonstrated that 46 of the 49 (94%) GISTs were immunopositive for c-KIT, 40 (82%) were CD34-positive, and 38 (78%) were positive for both c-KIT and CD34. Surrounding ICCs were also c-KIT/CD34-positive, suggesting that the GISTs had originated from ICCs.

CD117, the c-KIT proto-oncogene product, appears to be a sensitive and specific marker for GISTs. In an analysis of mesenchymal tumours by Sarlomo-Rikala et al (8), c-KIT-positive expression occurred in 85% of GISTs but was consistently negative in other tumour types, such as leiomyomas and Schwannomas, and was only occasionally detected in dermatofibrosarcomas protuberans and hemangiopericytomas. CD34 is a hematopoietic progenitor cell antigen. A number of tumour types, including fibrous tumours and Kaposi's sarcoma,



**Figure 2)** KIT gain-of-function mutations in gastrointestinal stromal tumours. TK Tyrosine kinase. Adapted from reference 16

were found to be CD34-positive, indicating that CD34 is somewhat less useful as a specific GIST marker.

Hirota et al (7) compared the complete coding region of c-KIT from GISTs with that of normal cells and identified mutations in the juxtamembrane domain (exon 11) of the c-KIT proto-oncogene in five of six GISTs. Lux et al (13) subsequently analyzed eight GISTs that lacked juxtamembrane mutations. Six of these eight cases had mutations in the extracellular domain (exon 9), while the other two had mutations in the TK domain (exon 13), which is associated with KIT tyrosine phosphorylation.

Heinrich et al (14) have recently reported that platelet-derived growth factor receptor-alpha (PDGFRA) gene mutations are found in approximately 5% of GISTs. PDGFRA is closely related in structure and function to c-KIT; therefore, PDGFRA mutations, in addition to the more prevalent c-KIT mutations, can be oncogenic. Approximately 20% of PDGFRA mutations involve the juxtamembrane domain and 80% involve the TK2 domain.

#### GIST pathogenesis

The alteration of transmembrane signalling receptor regulation is the initiating event in GISTs. The activation of c-KIT receptor TK is the central event in this process, and most commonly is the result of mutations of the cytoplasmic (exons 11, 13 and 17) or extracellular (exon 9) domains of the receptor (15). Mutations allow the uncharged c-KIT receptor to phosphorylate substrate proteins in the absence of ligand, initiating a signal transduction cascade that dysregulates cell proliferation, apoptosis, chemotaxis and adhesion.

Activating mutations in the c-KIT gene have been identified in a large majority of GISTs (9,16). In an analysis of 48 GISTs (10 benign, 10 borderline and 28 malignant cases), Rubin et al (9) reported that c-KIT mutations were present in 44 cases (92%). Of these, 34 (77% of the total) had mutations in the juxtamembrane region (exon 11), which likely has an autoinhibitory function that prevents phosphorylation (Figure 2). In six cases (13%), mutations occurred in the extracellular domain (exon 9), which probably drives dimerization; in four other cases, two different regions of the TK domain (exons 13 and 17) were affected. Other reports have confirmed that mutations in these TK domains are rare in GISTs (17). It was subsequently determined that, of the remaining four GISTs,

**TABLE 1**  
**Consensus guidelines for the prognosis of gastrointestinal stromal tumours**

Risk	Size (cm)	Mitotic count (per 50 HPF)	Survival (years)		
			5	10	15
Very low risk	<2	<5	98	85	75
Low risk	2 to 5	<5	90	70	40
Intermediate risk	<5	6 to 10	40	25	10
	5 to 10	<5	82	67	
High risk	>5	>10			
	>10	>5			

Adapted from reference 27. HPF High-power field

three had mutations of PDGFRA. Therefore, 47 of 48 GISTs in this series had a mutation to an identifiable TK mechanism.

### Benign versus malignant GISTs

Rubin et al (9) reported that c-KIT mutations were not confined to high-grade malignant GISTs but were also present in 'benign' tumours; it had been previously suggested that mutations occurred predominantly in malignant GISTs (18). c-KIT mutations have also been identified in small (4 mm to 10 mm) incidental GISTs; in this study (19), 11 of 13 tumours had c-KIT mutations, primarily in exon 11 (77%). In addition, germline mutations of c-KIT appear to be a cause of familial GISTs (20).

Thus, c-KIT mutations occur early in the pathogenesis of GISTs and would appear to precede any cytogenic alterations. c-KIT mutations may lead to benign hyperplasia of GIST progenitor cells, whereas subsequent acquisition of chromosomal deletions are responsible for neoplastic progression. A cytogenic analysis by Fukasawa et al (21) included 22 GISTs classified as high- and low-risk. Cytogenic deletions were detected in chromosomes 14 and 22. Similarly, Breiner et al (22) reported the loss of the entire chromosome 14 or regions of 14q, and of chromosome 22 or regions of 22q, in two-thirds of GISTs. These chromosomal losses may delete tumour suppressor genes and lead to tumour formation. Both of these studies found that loss of 14q and 22q occurred with similar frequency in high-risk (malignant) and low-risk (benign) tumours (21,22).

Loss of chromosome 1p can also be seen in both benign and malignant GISTs, but has been found to be more prevalent in malignant tumours (23). Likewise, aberrations of chromosomes 5p, 8q, 17q and 20q may be more frequent in malignant and metastatic GISTs (24). These findings indicate that malignant GISTs are characterized by more significant chromosomal changes (25).

These data indicate that the acquisition of characteristic cytogenic deletions occurs early in the natural history of GISTs and that there is a genetic continuum, whereby the number of mutations correlates with the degree of malignancy.

### ASSESSING MALIGNANT POTENTIAL

An estimated 25% to 30% of newly diagnosed GISTs are frankly malignant or have high malignant potential at presentation (26). While the majority of all GISTs have activating c-KIT mutations, the type and location of c-KIT mutations are only somewhat predictive of long-term

**TABLE 2**  
**Long-term survival of c-Kit-positive gastrointestinal stromal tumours**

	Survival (years)		
	5	10	15
Low risk, <5 cm, low grade, %	98	85	75
Intermediate risk, 5–10 cm, low grade, %	90	70	40
High risk, >10 cm, high grade, %	40	25	10
Overall, %	82	67	

Adapted from reference 27

outcome and their presence does not preclude a benign clinical course (10). Although it is now recognized that GISTs that were formerly classified as benign do have malignant potential (27), these tumours are now considered to be either low- or high-risk.

The prognosis of localized GIST is routinely estimated by tumour size and mitotic count (Tables 1 and 2) (28). In a retrospective analysis (29) of 200 GIST patients treated at one centre over a 16-year period, tumour size predicted disease-specific survival in patients who underwent complete resection. The five-year disease-free survival rate was 60% when the primary tumour was smaller than 5 cm in size, and 20% when the tumour was larger than 10 cm.

Similarly, a study (10) of 48 GIST patients followed for a median of 48 months reported that tumour size correlated with survival; median tumour size at study entry was 10 cm (range 2 cm to 30 cm). The five-year recurrence-free survival was 82% for patients with tumours smaller than 5 cm, 45% with tumours 5 cm to 10 cm, and 27% with tumours larger than 10 cm in size. Mitotic count and histology were also predictive of survival. The five-year recurrence-free survival rate was 89% for patients with tumours that had three or fewer mitoses per 30 high-power fields (HPF); 49% with three to 15 mitoses/30 HPF; and 16% with more than 15 mitoses/30 HPF. Patients with tumours demonstrating spindle cell histology had a 49% five-year disease-free survival, compared with 23% for patients with an epithelioid or mixed histology. The type and location of c-KIT mutation was also an independent predictor of disease-free survival in this study.

Mitotic counts are subject to high interobserver variability and may be supplemented by other measurements. The MIB-1 proliferation index, which uses a more objective stain as a marker of proliferation, has also been shown to be useful in differentiating benign from potentially or definitely malignant GISTs (3,30), although one group has reported that this technique is accurate only for gastric, and not for intestinal, GISTs (31).

Hasegawa et al (3) investigated 171 cases of GIST for a median follow-up period of 83.5 months. GISTs were evaluated using the MIB-1 grading system, which is based on tumour differentiation, MIB-1 score and the amount of necrosis. An MIB-1 grade 1 (in which the tumour is well-differentiated, lesions have 0% to 9% immunoreactive cells and there is less than 50% tumour necrosis) was considered to indicate a low-grade GIST. Grade 2 or 3 tumours were considered high-grade. The overall five and 10 year survival rates for low-grade GISTs were 81.7% and 67.4%, respectively.

**TABLE 3**  
**Response of gastrointestinal stromal tumours to imatinib**

	All doses (n=147)
Best response, n (%)	
Complete response	0 (0.0)
Partial response	59 (40.1)
Stable disease	61 (41.5)
Progressive disease	18 (12.2)
Not evaluable	7 (4.8)
Unknown	2 (1.4)

Adapted from reference 43

## TREATMENT OF RECURRENT OR METASTATIC GIST

### Surgery

Traditionally, the therapeutic options for GISTs were limited to surgical resection of the primary tumour and adjacent organs. While this approach may be curative, the long-term recurrence rate has been estimated at 90% (32). The five-year survival rate for patients following complete resection is approximately 40% (33,34). In a review of 50 cases of localized, locally advanced or metastatic small intestinal GISTs by Crosby et al (33), complete resection significantly improved overall survival. In this study, the stage of the tumour at presentation, but not the tumour grade, was a significant prognostic factor.

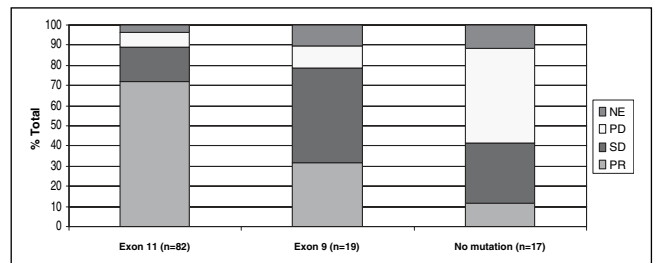
The optimal surgical approach is difficult to determine from the literature because of the small number of cases reported, differences in clinical variables, lack of intra-abdominal compartment, lack of consistency in the approach to management and the differing follow-up protocols (35).

### Imatinib

Conventional chemotherapy and radiotherapy are generally ineffective for residual, recurrent or metastatic disease, with response rates of less than 5% (36-38).

The management of GISTs was revolutionized by the introduction of imatinib, an inhibitor of c-KIT, PDGFR and Abelson TK proteins. Following an initial report of a favourable response to imatinib (39), its safety and efficacy were examined in a phase I trial of 40 patients with metastatic soft tissue sarcomas (40), of whom 36 (90%) were c-KIT-positive. Patients received imatinib 400 mg once daily, 300 mg twice daily or 500 mg twice daily. Patients in the 500 mg twice daily arm experienced dose-limiting toxicities; the maximum tolerated dose was 400 mg twice a day. Of the 35 evaluable GIST patients, 19 (54%) had a partial response and 13 (37%) had stable disease with imatinib (40,41). At 10 month follow-up, 18 patients (51%) continued to have partial responses and 11 (31%) had stable disease (41). Treatment was generally tolerated well. The most common adverse effects were periorbital edema, peripheral edema, fatigue, skin rash and nausea/vomiting.

In a multicentre open-label phase II trial involving 147 patients with metastatic or unresectable malignant GISTs (42), imatinib 400 mg/day or 600 mg/day produced a major response in 79 patients (53.7%) (Table 3). A total of 80% of patients enjoyed a treatment benefit (eg, a partial response or tumour stabilization). Clinical improvement was generally rapid: 22% of patients responded at four weeks and 54% at 12 weeks,



**Figure 3)** Correlation of imatinib clinical response with KIT mutation. NE Not evaluable; PD Progressive disease; PR Partial response: tumour mass less than 50% of starting size; SD Stable disease: tumour mass 50% to 100% of starting size

and 58 of the 59 patients with partial response showed a durable response during the follow-up period (seven to 38 weeks). The estimated one-year survival rate was 88%.

**Imatinib response versus nonresponse:** As noted previously, activation of the c-KIT receptor is the central pathogenic event in the majority of GISTs, with activation resulting from oncogenic point mutations occurring either intracellularly (juxta-membrane or TK domains) or extracellularly (dimerization domain). Over 90% of GISTs are c-KIT-positive (7,43).

Imatinib inhibits c-KIT enzymatic activity, thereby blocking tyrosine phosphorylation and preventing GIST cell proliferation. These effects may tip the balance in favour of apoptotic cell death over proliferation in malignant GISTs (43,44).

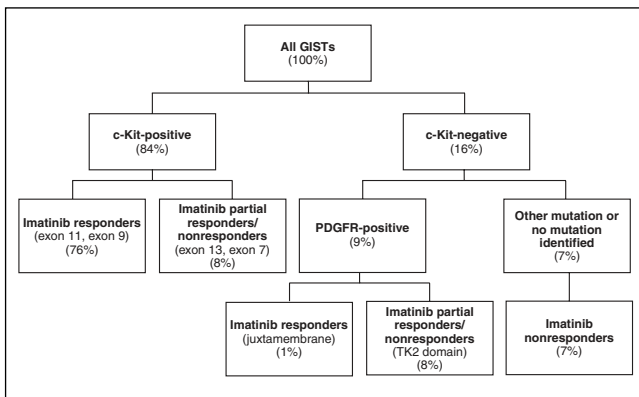
Accordingly, imatinib response is correlated with mutations in the juxtamembrane domain (exon 11). In these patients, who constitute 77% of all GIST cases (Figure 3), one-year survival has been estimated to be as great as 95%. A partial response may also be observed in the 13% of c-KIT-positive patients with an extracellular mutation (exon 9), with a one-year survival of up to 85%. These results compare favourably with the 40% one-year survival rate in historic controls.

As Heinrich et al (14) noted, among GISTs with no demonstrable c-KIT mutation, approximately 30% have mutations of another TK, the PDGFR. Approximately 20% of this subset of cases have PDGFR mutations in the juxtamembrane domain and would be expected to respond to imatinib; the remaining 80% of this group have mutations in the TK2 domain (D842V) and would be expected to be unresponsive. Thus, the expected overall response to imatinib would be 71%, with a partial response in a further 20% of patients and no response in the other 9% (Figure 4).

Nevertheless, imatinib is recommended for all patients with inoperable malignant or recurrent GISTs, including those who are c-KIT-negative or c-KIT-positive with no identifiable mutations, because such patients may achieve a partial response and/or symptomatic improvement. Imatinib responders should be continued on therapy indefinitely because long-term treatment does not appear to promote resistance and tumours often progress rapidly after imatinib is discontinued. An increase in the imatinib dosage does not appear to be effective for cases of disease progression.

**Progression and the development of resistance:** Four principal mechanisms for the development of resistance to imatinib have been proposed (45):

- 1. Acquired mutations:** A previously stable or responding GIST may subsequently develop a c-KIT (eg, an exon 17



**Figure 4)** Molecular profile of potential imatinib responders. GIST Gastrointestinal stromal tumour; PDGFR Platelet-derived growth factor receptor

mutation [D816H] in the TK2 domain, which is also found in mast cell disease and seminoma) that is resistant to imatinib.

- Target overexpression:** A previously stable or responding GIST may subsequently develop genomic amplification, thus giving rise to overexpression of the altered c-KIT oncogene, which produces too many targets for imatinib to inhibit.
- Target modulation:** A c-KIT-positive GIST may undergo alterations that result in the activation of alternative receptor TK proteins and the loss of c-KIT protein expression. Furthermore, there may be activation of other receptor TK proteins, which can substitute for c-KIT in driving GIST proliferation (46).
- Functional resistance:** Progression may be due to activating c-KIT mutations outside the juxtamembrane region of c-KIT or PDGFR (eg, exon 18 D842V), which in turn activate downstream signalling pathways.

#### Role of surgery with imatinib

Surgery remains the primary treatment modality with the goal of achieving a complete resection. With recurrent or metastatic GISTs, resection of distant metastases to alleviate symptoms may be advised if technically feasible.

The use of imatinib therapy before surgery may reduce tumour bulk and prevent metastasis. Studies are currently being done to test this hypothesis. Treatment should be continued for the duration of the illness if there is a clinical response. Partial responders to imatinib should be evaluated early for resection, because surgery may no longer be advisable later in the disease course (47).

Other treatment options, such as radiofrequency ablation of liver metastases, embolization or peritoneal perfusion, are still considered experimental and are generally reserved for patients who are resistant to imatinib.

#### Role of imatinib in adjuvant or neoadjuvant management of GISTs

Few studies have explored the role of imatinib as adjuvant or neoadjuvant therapy, but large clinical trials are currently being undertaken to examine this possibility. A preliminary report suggested that it may be beneficial before surgery for progressive disease (47). Although the idea is very attractive,

imatinib is not yet recommended or approved in the adjuvant or neoadjuvant setting.

#### SUMMARY AND CONCLUSIONS

- GISTs are rare GI tumours that have been generally inadequately recognized, and the natural history of GISTs is poorly understood.
- GISTs are morphologically and immunophenotypically similar to ICCs and are believed to originate from cells that would normally differentiate into that phenotype.
- The recognition of c-KIT in GISTs is an important advance in distinguishing GISTs from other GI sarcomas. Over 90% of GISTs stain for c-KIT.
- All GISTs have the potential to be malignant. Approximately one-third are malignant at presentation; the remainder may be classified as low- or high-risk.
- Tumour size, mitotic index or surrogate markers, such as MIB-1, remain the most reliable methods of detecting malignancy.
- Surgical resection remains the first-line treatment of GISTs.
- Imatinib, a receptor TK inhibitor, is an important addition to the armamentarium for inoperable, metastatic or recurrent GISTs.

The dramatic results of the targeted molecular therapy imatinib for GIST raise a number of important clinical questions about the diagnosis and management of GISTs that could not be entertained a few years ago, including:

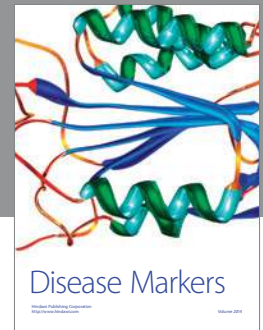
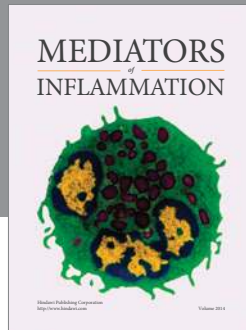
- In the immunohistochemical evaluation of GISTs, is there a need to standardize laboratory methods and procedures? How would immunohistochemical best be standardized? What is the minimally positive control that should be used?
- Is there a need to quantitate the intensity of CD117 staining?
- Is there value in resecting stable residual disease following response to imatinib therapy in patients with metastatic disease?
- How do we evaluate the ongoing efficacy of imatinib? What are the response criteria? Is the presence of any immunoreactivity predictive of a response?
- What are the efficacy and safety of imatinib during long-term use?
- Can we control micrometastatic disease with imatinib? In other words, what is the role of imatinib in the adjuvant or neoadjuvant setting?

Additional research and clinical experience are needed to resolve these and other issues regarding the optimal management of GISTs.

The development of a selective receptor TK inhibitor is a major advance in our treatment of GISTs, and the characterization of the molecular genetics of these tumours should assist clinicians in predicting a response to imatinib. Opportunities exist for novel therapies that target alternative receptor TKs, or other downstream components of the signalling cascade.

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