Personalized Medicine Review Series *J. Cell. Mol. Med. Vol 14, No 1-2, 2010 pp. 42-50*

Guest Editors: R. Osamura & A. Gown

Imatinib treatment for gastrointestinal stromal tumour (GIST)

Lisandro F. Lopes, Carlos E. Bacchi *

Consultoria em Patologia, Botucatu, SP, Brazil

Received: October 1, 2009; Accepted: November 20, 2009

Abstract

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. GISTs are believed to originate from interstitial cells of Cajal (the pacemaker cells of the gastrointestinal tract) or related stem cells, and are characterized by *KIT* or *platelet-derived growth factor receptor alpha (PDGFRA)* activating mutations. The use of imatinib has revolutionized the management of GIST and altered its natural history, substantially improving survival time and delaying disease progression in many patients. The success of imatinib in controlling advanced GIST led to interest in the neoadjuvant and adjuvant use of the drug. The neoadjuvant (preoperative) use of imatinib is recommended to facilitate resection and avoid mutilating surgery by decreasing tumour size, and adjuvant therapy is indicated for patients at high risk of recurrence. The molecular characterization (genotyping) of GISTs has become an essential part of the routine management of the disease as *KIT* and *PDGFRA* mutation status predicts the likelihood of achieving response to imatinib. However, the vast majority of patients who initially responded to imatinib will develop tumour progression (secondary resistance). Secondary resistance is often related to secondary *KIT* or *PDGFRA* mutations that interfere with drug binding. Multiple novel tyrosine kinase inhibitors may be potentially useful for the treatment of imatinib-resistant GISTs as they interfere with KIT and PDGFRA receptors or with the downstream-signalling proteins.

Keywords: gastrointestinal stromal tumour • GIST • imatinib • KIT • mutation • PDGFRA • sunitinib

Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract, comprising the majority of tumours previously diagnosed as leiomyomas, leiomyoblastomas, leiomyosarcomas, neurofibromas and schwannomas. GISTs are believed to originate from intersticial cells of Cajal (the pacemaker cells of the gastrointestinal tract) or related stem cells, and are characterized by *KIT* or *platelet-derived growth factor receptor alpha (PDGFRA)* activating mutations [1–6].

Recent population-based studies in Europe revealed annual incidences of 10–20 per million, and the prevalence was estimated at 129 per million [7–9]. About 4500–6000 new cases of GIST are diagnosed each year in the USA [10].

GISTs have an equal sex predilection, and most tumours occur in individuals over the age of 50. GISTs are very rare in children (<1%) [1, 2, 11, 12].

GIST occurs throughout the gastrointestinal tract. The most common sites are the stomach (50%) and small bowel (25%). Approximately 10% of GISTs arise in the colon and rectum and 5% within the oesophagus. About 10% of the cases occur outside of the gastrointestinal tract (extra-gastrointestinal GISTs), mainly in the mesentery, omentum, retroperitoneum and pelvis [1, 2, 13–20].

The most common clinical presentation of GIST is gastrointestinal bleeding. Acute abdomen due to tumour rupture, obstruction, appendicitis-like pain, early satiety, bloating or fatigue related to anaemia can occur. Smaller GISTs are often incidental findings during surgery, radiologic studies or endoscopic procedures. Aggressive tumours generally metastasize to the liver or disseminate throughout the abdomen, and they rarely metastasize to lymph nodes or spread outside of the abdominal cavity [1, 2, 13].

*Correspondence to: Carlos E. BACCHI, M.D., Ph.D.,
Consultoria em Patologia,
Rua Major Leonidas Cardoso, 739, Botucatu,
SP, 18602-010, Brazil.
Tel./Fax: +55 14 31125900
E-mail: bacchi@conspat.com.br

doi:10.1111/j.1582-4934.2009.00983.x

GISTs range in size from less than 10 mm (GIST tumorlets) to very large lesions (>350 mm), and the median size is approximately 50 mm. Small GISTs often form solid subserosal, intramural or polypoid intraluminal masses. Larger GISTs form external, pedunculated masses attached to outer aspect of gastrointestinal structures. They are usually uninodular but multiple nodules may occur. Cystic degeneration, haemorrhage or necrosis can be found, generally in larger tumours [1, 2].

GISTs are usually cytologically monomorphic and exhibit spindle cell or epithelioid cell cytomorphology, as well as a mixed pattern consisting of both spindle and epithelioid cells [10]. Epithelioid and mixed spindle and epithelioid GISTs are more common in the stomach [16]. Spindle cell GISTs are generally arranged in fascicles, and epithelioid tumours are often arranged in nests or sheets. The stroma can be hyalinized or myxoid. Histological features that can be seen in GISTs are paranuclear vacuoles, nuclear palisading mimicking schwannoma, neuroendocrine-like morphology mimicking paraganglioma or carcinoid tumour, and 'skeinoid' fibres, hyaline eosinophilic cytoplasmic structures that are found predominantly in small bowel GISTs [1, 2, 13].

Approximately 96% of GISTs are positive for KIT (CD117) by immunohistochemistry. CD34 can be expressed by 60–70% of the tumours, and smooth muscle actin (SMA) expression is detected in 30–40% of the cases. S100 protein, keratins and desmin are rarely expressed in GISTs (up to 5%) [1–3, 10, 13, 21–23]. Recently, gene expression profiling studies found that the DOG1 ('Discovered On GIST-1') protein was ubiquitously expressed in GISTs, regardless of mutation status [24]. Subsequently, several studies found that DOG1 is a sensitive immunohistochemical marker for GIST, being rarely expressed in other mesenchymal tumours [25–27].

The main differential diagnosis of GIST includes smooth muscle tumours (leiomyoma and leiomyosarcoma), nerve sheath tumours (schwannoma and neurofibroma), inflammatory fibroid polyp and desmoid fibromatosis. These tumours are almost invariably negative for KIT (CD117) by immunohistochemistry. Moreover, smooth muscle tumours and nerve sheath tumours are diffusely positive for desmin and S100 protein, respectively. Inflammatory fibroid polyp can be positive for CD34, but there is no expression of KIT. Desmoid fibromatosis generally expresses fl-catenin in the nuclei of the spindle cells. It is important to state that KIT (CD117) is not expressed by GIST only. Other tumours that are consistently KIT-positive are mastocytoma, seminoma and granulocytic sarcoma. Melanoma, Ewing sarcoma family of tumours, angiosarcoma and some carcinomas can also express KIT [1, 2, 28, 29].

It is generally agreed that the most important prognostic factors in GIST are size of the tumour and mitotic count, which defines the risk of aggressive behaviour. The most commonly used scheme to assess such risk is the National Institutes of Health (NIH) consensus approach [10]. However, it is known that tumours arising in the intestines are generally associated with less favourable outcome than those arising in the stomach with similar size and mitotic index parameters (see Table 1) [15, 30]. Patients whose tumour has ruptured into the abdominal cavity have a high risk of tumour recurrence [31].

Surgery is the standard treatment for all non-metastatic GISTs. Regional lymph node resection is of no value as GISTs rarely give rise to lymph node metastases. The tumour should be removed *en bloc* with its pseudocapsule to yield an adequate resection margin. Imatinib, a tyrosine kinase inhibitor of KIT and PDGFRA receptors, is considered as the standard treatment for metastatic and/or unresectable GIST. The neoadjuvant use of imatinib is recommended to avoid mutilating surgery and/or yield complete resection of the tumour. Adjuvant treatment with imatinib may benefit patients presenting high risk of recurrence of the tumour after surgery [32–36]. Sunitib, a multiple tyrosine kinase inhibitor, may be useful for the treatment of GIST after disease progression under imatinib therapy or intolerance to imatinib [37].

Molecular pathogenesis of GIST

KIT and *PDGFRA* genes, located pericentromerically at 4q11-q12, encode for similarly named highly homologous receptor tyrosine kinase proteins (KIT and PDGFRA) [38]. KIT and PDGFRA have structural characteristics of type III receptor tyrosine kinase family [39]. Activating mutations of *KIT* and *PDGFRA* genes permit ligand-independent phosphorylation of the receptor tyrosine kinases, perpetuating the receptor-initiated signal and causing activation of the downstream effectors (Fig. 1). Increase in cellular proliferation and decrease in apoptosis are the end results of such activation, ultimately leading to enhanced cell survival and the development of neoplasia. Mutually exclusive mutations in *KIT* or *PDGFRA* are observed in more than 80% of GISTs (see Table 2) [4, 40, 41].

KIT contains a total of 21 exons, but mutations can be mainly detected in four exons: 9, 11, 13 and 17. Exon 9 encodes the extracellular transmembrane domain of KIT receptor. Exon 11 encodes the intracellular juxtamembrane domain. Exons 13 and 17 encode the tyrosine kinase domain: the first portion of the split kinase domain in encoded by exon 13, while exon 17 encodes the kinase activation loop (second tyrosine kinase domain) [4, 42, 43]. *KIT* exon 11 mutations are the most common (60–70% of GISTs), mainly in-frame deletions of variable sizes, but substitutions (point mutations), duplications and insertions may occur. Exon 9 mutations are the second most common and are detected in 10% of GISTs, most of them located in the small bowel. Exon 9 mutations represent mainly in-frame tandem duplication (Ala502_Tyr503dup). Substitutions have been reported in *KIT* exons 13 and 17, but primary mutations in those exons are rare (up to 2% of GISTs) [1, 2, 4, 5, 41, 43–48].

Approximately 5–10% of GISTs have *PDGFRA* mutations instead of *KIT* mutations. The mutations that are found in *PDGFRA* involve exon 18 (second tyrosine kinase domain), exon 12 (juxtamembrane domain) and exon 14 (first tyrosine kinase domain). Exon 18 mutations are the most common (up to 6% of GISTs),

Table 1 Assessment of risk of aggressive behaviour in GIST by mitotic index, size and tumour location

Morphologic parameters		% of patients with progressive disease			
Size (cm)	**Mitotic index**	**Stomach**	**Jejunum/ileum**	**Duodenum**	**Rectum**
≤2	≤5/50 HPFs	0	0	0	0
>2 and ≤5	≤5/50 HPFs	1.9	4.3	8.3	8.5
>5 and ≤10	≤5/50 HPFs	3.6	24	34*	57*
>10	≤5/50 HPFs	12	52		
≤2	>5/50HPFs	0	50	–	54
>2 and ≤5	>5/50HPFs	16	73	50	52
>5 and ≤10	>5/50HPFs	55	85	86*	71*
>10	>5/50HPFs	86	90		

Modified from Miettinen and Lasota, 2006 [30].
HPFs, high-power fields.
* >5 and ≤10 cm and >10 cm groups are combined because of small number of cases.

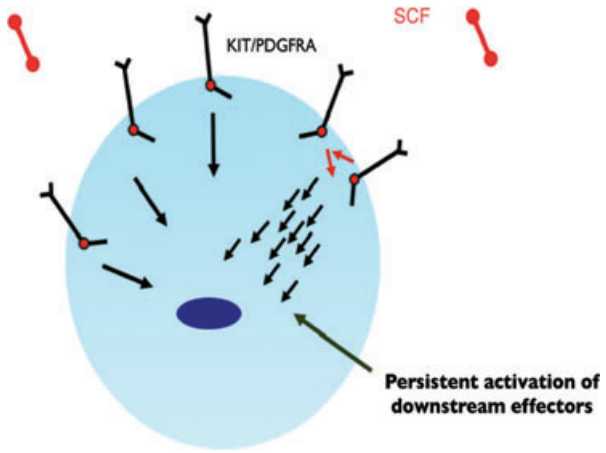

Fig. 1 Schematic representation of molecular pathogenesis of GIST. Activating mutations of *KIT* and *PDGFRA* genes permit phosphorylation of KIT/PDGFRA receptor tyrosine kinases independent of ligand SCF (stem cell factor), perpetuating the receptor-initiated signal and causing activation of the downstream effectors. The result is enhanced cell survival.

Table 2 Molecular classification of GIST

Genotype	Frequency	Tumour location
KIT mutation	70–80%	
Exon 9	10%	Small bowel, colon
Exon 11	60–70%	All sites
Exon 13	1%	All sites
Exon 17	1%	All sites
PDGFRA mutation	5–10%	
Exon 12	1%	All sites
Exon 14	<1%	Stomach
Exon 18 D842V	5%	Stomach, mesentery, omentum
Exon 18 (other than D842V)	1%	All sites
Wild-type	10–15%	All sites

while exon 12 and exon 14 mutations are rarely found (< 2% of GISTs). Single nucleotide substitutions are the most common *PDGFRA* mutations in GIST. In exon 18, the most common mutation is a single nucleotide substitution known as Asp842Val (D842V). In-frame deletions have also been detected in exon 18. *PDGFRA* exons 12 and 14 mutations involve substitutions, insertions and deletions [1, 2, 6, 48–50]. *PDGFRA* mutations show a strong predilection for the stomach, epithelioid morphology, myxoid stroma, nuclear pleomorphism and variable (occasionally absent) expression of KIT (CD117) [1, 2, 6, 13, 22, 51–55].

No *KIT* or *PDGFRA* mutation is detected in 10–15% of GISTs (wild-type GISTs). Notably, wild-type genotype is a characteristic feature of the vast majority of GISTs diagnosed in children and adolescents and GISTs associated with familial syndromes such as neurofibromatosis, Carney–Stratakis syndrome or the Carney triad [41]. The molecular biology that drives the growth of wild-type GISTs is incompletely understood, but the KIT tyrosine kinase appears to be activated (phosphorylated KIT) in many of these tumours despite lack of detectable KIT mutation. An activating mutation either in a receptor tyrosine kinase that is analogous to

KIT and PDGFRA or in a downstream signalling molecule of the KIT/PDGFRA signalling cascade could be involved. Recently, a primary *BRAF* V600E mutation was detected in 7% of adult GIST patients lacking *KIT/PDGFRA* mutations. The *BRAF*-mutated GISTs showed predilection for small bowel location and high risk of malignancy [1, 56, 57].

Imatinib and implications of mutation status for the treatment of GIST

The use of imatinib has revolutionized the management of unresectable and metastatic GISTs and altered its natural history, substantially improving survival time and delaying disease progression in many patients [58, 59].

Imatinib (STI571) was the first targeted therapy approved for the treatment of GIST, and it has become the treatment of choice for advanced GIST. Imatinib is an orally available tyrosine kinase inhibitor of KIT and PDGFRA receptors first developed as a treatment for chronic myeloid leukemia by inhibiting the intracellular kinases ABL and BCR-ABL fusion protein [60–63]. Imatinib blocks the transfer of phosphate groups from adenosine triphosphate to tyrosine residues of the substrates. This results in interruption of the downstream signalling cascade that regulates cell proliferation (Fig. 2) [63].

Imatinib is considered as the standard treatment of metastatic GIST. A partial response is observed in approximately 65–70% of the patients, and 15–20% have stable disease. Only 5% or less achieve a complete response. The median response duration exceeds 2 years [59, 64]. The standard starting dose of imatinib is 400–600 mg daily, even though 600 mg proved not to be superior to 400 mg [59], and continuous administration of imatinib is recommended in the treatment of advanced disease with no upper limit for treatment duration as discontinuation of treatment was associated with disease progression. Only tumour progression, intolerance or patient refusal should encourage interruption of treatment [65].

Response monitoring is carried out using computed tomography (CT), magnetic resonance imaging (MRI) and/or metabolic imaging with fluorodeoxyglucose-positron emission tomography (FDG-PET). GIST liver metastases generally turn into hypodense lesions with cystic degeneration on CT scans [66].

Adverse effects of imatinib therapy are usually mild to moderate. The most common are oedema (particularly periorbital), muscle cramps in fingers and feet, diarrhoea, nausea and vomiting, fatigue and rash. Haematological disturbances may occur, including anaemia and neutropenia. Elevation in liver transaminase levels is also common [32].

The success of imatinib in controlling advanced GIST led to interest in the neoadjuvant and adjuvant use of the drug. The neoadjuvant (preoperative) use of imatinib is recommended to facilitate resection and avoid mutilating surgery by decreasing tumour size. The use of neoadjuvant imatinib therapy was considered safe with encouraging outcomes [58, 67–73]. Adjuvant therapy is indicated for patients at high risk of recurrence. It was demonstrated that imatinib at 400 mg daily for 1 year following surgical resection prolongs recurrence-free survival and is associated with improved overall survival [58, 73–75].

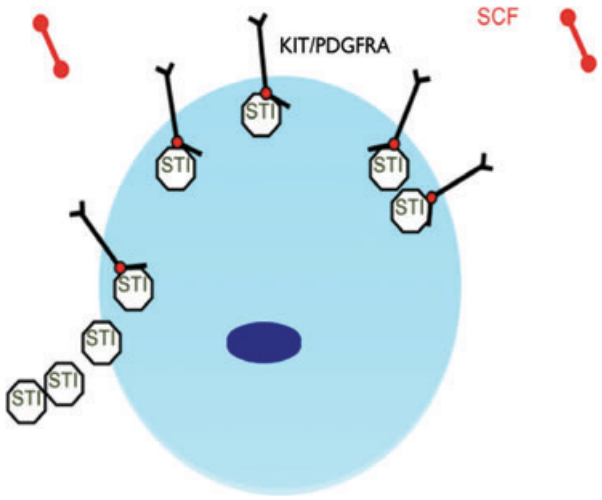

Fig. 2 Role of imatinib in the treatment of GIST. Imatinib interrupts the downstream signalling cascade that regulates cell proliferation by blocking the transfer of phosphate groups from adenosine triphosphate to tyrosine residues of the substrates.

Pathologists play an important role in the molecular characterization (genotyping) of GISTs. GIST genotyping has become an essential part of the routine management of the disease as *KIT* and *PDGFRA* mutation status predicts the likelihood of achieving response to imatinib. Clinical observations have shown that *KIT* exon 11 mutations are associated with better response to imatinib and longer progression-free survival than *KIT* exon 9 mutations and wild-type genotype. Thus, patients with GISTs presenting *KIT* exon 9 mutation require a higher dosage of imatinib (800 mg daily instead of the standard dose of 400 mg daily) in order to achieve similar therapeutic results. *PDGFRA* exon 18 Asp842Val (D842V) mutation is resistant to imatinib treatment. *PDGFRA* mutations other than Asp842Val (D842V) may be sensitive to imatinib [48–50, 76, 77].

In conclusion, routine tumour genotyping is recommended if tyrosine kinase inhibition therapy is considered for the treatment of GIST.

Imatinib resistance in GIST

A minority of patients (10–20%) experience tumour growth on imatinib within the first 6 months of treatment (primary resistance), and *PDGFRA* D842V and *KIT* exon 9 (under standard imatinib

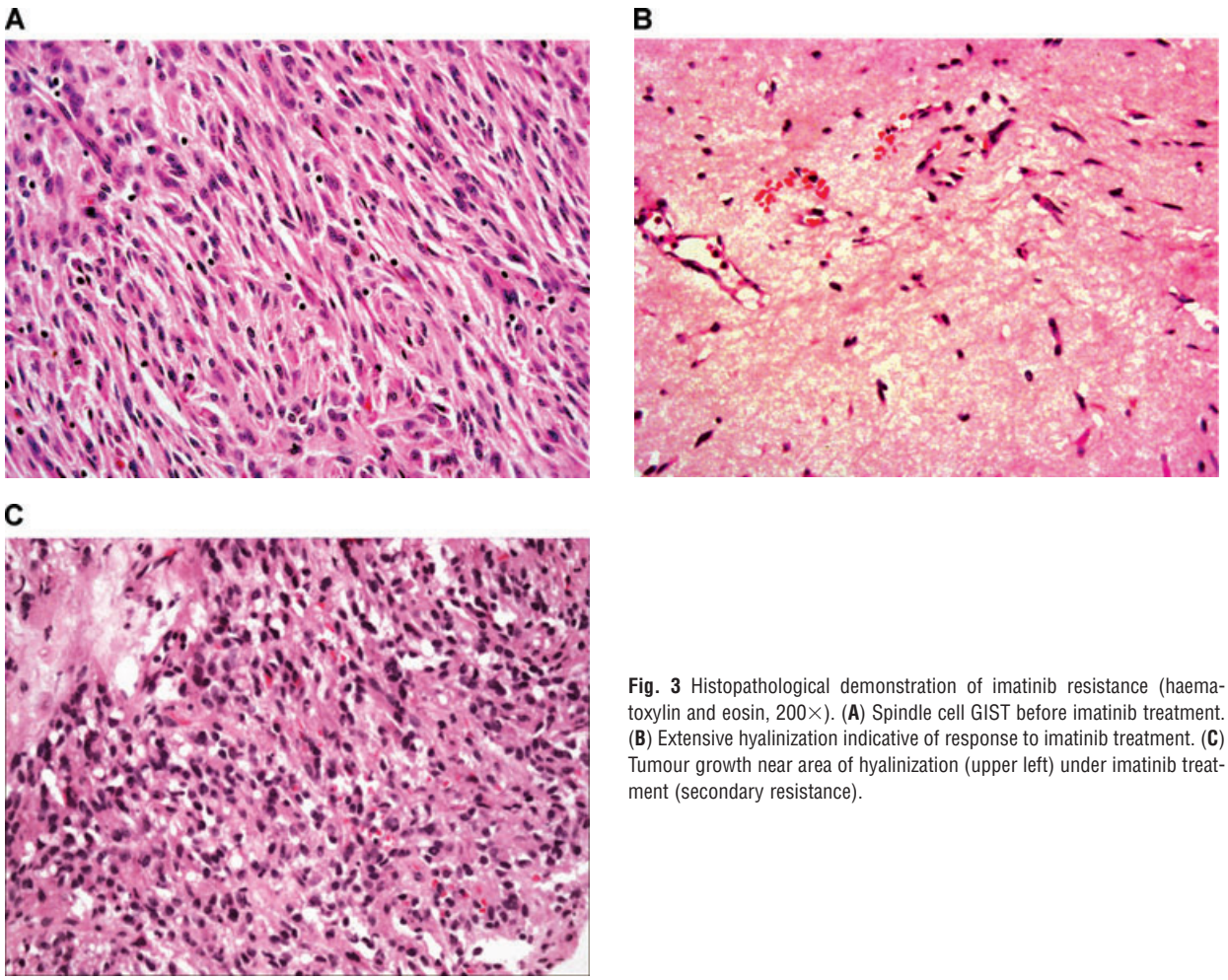

Fig. 3 Histopathological demonstration of imatinib resistance (haematoxylin and eosin, 200×). (**A**) Spindle cell GIST before imatinib treatment. (**B**) Extensive hyalinization indicative of response to imatinib treatment. (**C**) Tumour growth near area of hyalinization (upper left) under imatinib treatment (secondary resistance).

dose therapy) mutations as well as wild-type genotype may explain primary resistance. However, the causes for such resistance remain largely unknown [58].

The vast majority of patients who responded to imatinib will develop tumour progression (secondary resistance). Secondary resistance (Fig. 3) often develops due to secondary *KIT* or *PDGFRA* mutations that interfere with drug binding. Most secondary *KIT* mutations represent single nucleotide substitutions affecting codons in exons 13, 14, 15, 16 and 17. Secondary *PDGFRA* mutations involve exon 18 (Asp842Val). Interestingly, GISTs with primary *KIT* mutations in exon 11 (tumours with better response rates than other genotypes) reveal secondary mutations more frequently in comparison to tumours with *KIT* exon 9 mutations, suggesting that the development of secondary *KIT* mutations is an important escape mechanism for tumour cells. Moreover, several different types of mutations may occur independently indicating polyclonal resistance [48, 78–84].

Another possible mechanism of imatinib resistance is *KIT* gene amplification [79], and other oncogenes and tumour suppressor genes may also be responsible for sustaining the tumourigenic potential in imatinib-resistant GISTs. Moreover, the constitutive activation of downstream-signalling proteins (kinase pathways) represents a distinct molecular mechanism of imatinib resistance, and the PI3-kinase/AKT may play an important role as an alternate survival pathway [81, 85].

Multi-targeted tyrosine kinase inhibitors for the treatment of GIST

Multiple novel tyrosine kinase inhibitors may be potentially useful for the treatment of imatinib-resistant GISTs as they interfere with KIT and PDGFRA receptors or with the downstream-signalling proteins [86].

Sunitinib (SU11248) was approved for the treatment of imatinib-resistant GIST or imatinib-intolerant patients. Sunitinib

inhibits multiple receptor tyrosine kinases including KIT, PDGFRA, platelet-derived growth factor receptor beta (PDGFRB), vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, FMS-related tyrosine kinase 3 receptor, receptor for macrophage colony-stimulating factor and glial cell line-derived neurotrophic factor receptor, presenting both antiangiogenic and antiproliferative activities. Sunitinib is indicated for patients whose disease progressed on imatinib (even after imatinib dose escalation up to 800 mg daily), and it presents better responses in wild-type genotype tumours and GISTs with *KIT* exon 9 mutation or secondary *KIT* mutations (exons 13 or 14). The drug is orally available, and the approved schedule is 50 mg per day for 4 weeks followed by a 2-week rest. The most common adverse effects include diarrhoea, mucositis, hair and skin discoloration, high blood pressure, bleeding and fatigue [33, 37, 87–92].

Other candidate tyrosine kinase inhibitors are being tested, including nilotinib, dasatinib, sorafenib, masitinib, vatalanib (PTK787/ZK222584) and motesanib (AMG 706) [36, 93–101].

The PKC inhibitor PKC412, the rapamycin target protein (mTOR in the AKT pathway) inhibitor everolimus and the heat shock protein 90 (HSP90) inhibitor IPI-504 may also turn out to have efficacy in the treatment of GIST [36, 79, 102].

Conclusion

The management of GIST has experienced rapid progress since it was recognized as a distinct tumour entity. The introduction of imatinib revolutionized the treatment of the disease, and it has led to important improvements in quality of life and survival of the patients. GIST mutation analysis (genotyping) has emerged as a major factor in the evaluation of GIST, particularly for advanced tumours or those that have high risk of recurrence, which may benefit from imatinib. Genotyping can help in deciding on imatinib dose, in estimating the likelihood of benefit, and potentially selecting second-line therapy with other promising tyrosine kinase inhibitors.

References

1. **Rubin BP.** Gastrointestinal stromal tumours: an update. *Histopathology*. 2006; 48: 83–96.
2. **Miettinen M, Lasota J.** Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med*. 2006; 130: 1466–78.
3. **Kindblom LG, Remotti HE, Aldenborg F, *et al.*** Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol*. 1998; 152: 1259–69.
4. **Hirota S, Isozaki K, Moriyama Y, *et al.*** Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science*. 1998; 279: 577–80.
5. **Corless CL, McGreevey L, Haley A, *et al.*** KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. *Am J Pathol*. 2002; 160: 1567–72.
6. **Heinrich MC, Corless CL, Duensing A, *et al.*** PDGFRA activating mutations in gastrointestinal stromal tumors. *Science*. 2003; 299: 708–10.
7. **Nilsson B, Bümming P, Meis-Kindblom JM, *et al.*** Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era–a population-based study in western Sweden. *Cancer*. 2005; 103: 821–9.
8. **Tryggvason G, Gíslason HG, Magnússon MK, *et al.*** Gastrointestinal stromal tumors in Iceland, 1990–2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer*. 2005; 117: 289–93.
9. **Mucciarini C, Rossi G, Bertolini F, *et al.*** Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. *BMC Cancer*. 2007; 7: 230.
10. **Fletcher CD, Berman JJ, Corless C, *et al.*** Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol*. 2002; 33: 459–65.
11. **Prakash S, Sarran L, Socci N, *et al.*** Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. *J Pediatr Hematol Oncol*. 2005; 27: 179–87.
12. **Miettinen M, Lasota J, Sobin LH.** Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. *Am J Surg Pathol*. 2005; 29: 1373–81.
13. **Lopes LF, Ojopi EB, Bacchi CE.** Gastrointestinal stromal tumor in Brazil: clinicopathology, immunohistochemistry, and molecular genetics of 513 cases. *Pathol Int*. 2008; 58: 344–52.
14. **Miettinen M, Furlong M, Sarlomo-Rikala M, *et al.*** Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. *Am J Surg Pathol*. 2001; 25: 1121–33.
15. **Miettinen M, Makhlouf H, Sobin LH, *et al.*** Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol*. 2006; 30: 477–89.
16. **Miettinen M, Sobin LH, Lasota J.** Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005; 29: 52–68.
17. **Miettinen M, Kopczynski J, Makhlouf HR, *et al.*** Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. *Am J Surg Pathol*. 2003; 27: 625–41.
18. **Miettinen M, Sarlomo-Rikala M, Sobin LH, *et al.*** Gastrointestinal stromal tumors and

leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases. *Am J Surg Pathol.* 2000; 24: 1339–52.

19. **Miettinen M, Monihan JM, Sarlomo-Rikala M, *et al.*** Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. *Am J Surg Pathol.* 1999; 23: 1109–18.
20. **Reith JD, Goldblum JR, Lyles RH, *et al.*** Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. *Mod Pathol.* 2000; 13: 577–85.
21. **Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, *et al.*** CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. *Mod Pathol.* 1998; 11: 728–34.
22. **Medeiros F, Corless CL, Duensing A, *et al.*** KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol.* 2004; 28: 889–94.
23. **Mikhael AI, Bacchi CE, Zarbo RJ, *et al.*** CD34 expression in stromal tumors of the gastrointestinal tract. *Appl Immunohistochem.* 1994; 2: 89–93.
24. **West RB, Corless CL, Chen X, *et al.*** The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. *Am J Pathol.* 2004; 165: 107–13.
25. **Espinosa I, Lee CH, Kim MK, *et al.*** A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. *Am J Surg Pathol.* 2008; 32: 210–8.
26. **Liegl B, Hornick JL, Corless CL, *et al.*** Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. *Am J Surg Pathol.* 2009; 33: 437–46.
27. **Miettinen M, Wang ZF, Lasota J.** DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. *Am J Surg Pathol.* 2009; 33: 1401–8.
28. **Miettinen M, Lasota J.** Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch.* 2001; 438: 1–12.
29. **Carlson JW, Fletcher CD.** Immunohistochemistry for beta-catenin in the differential diagnosis of spindle cell lesions: analysis of a series and review of the literature. *Histopathology.* 2007; 51: 509–14.
30. **Miettinen M, Lasota J.** Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006; 23: 70–83.
31. **Joensuu H.** Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol.* 2008; 39: 1411–9.
32. **Joensuu H.** Gastrointestinal stromal tumor (GIST). *Ann Oncol.* 2006; 17: x280–6.
33. **Judson I, Demetri G.** Advances in the treatment of gastrointestinal stromal tumours. *Ann Oncol.* 2007; 18: x20–4.
34. **ESMO Guidelines Working Group, Blay JY, Le Cesne A.** Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2007; 18: ii27–9.
35. **Din OS, Woll PJ.** Treatment of gastrointestinal stromal tumor: focus on imatinib mesylate. *Ther Clin Risk Manag.* 2008; 4: 149–62.
36. **Dirnhofer S, Leyvraz S.** Current standards and progress in understanding and treatment of GIST. *Swiss Med Wkly.* 2009; 139: 90–102.
37. **Goodman VL, Rock EP, Dagher R, *et al.*** Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res.* 2007; 13: 1367–73.
38. **Stenman G, Eriksson A, Claesson-Welsh L.** Human PDGFA receptor gene maps to the same region on chromosome 4 as the KIT oncogene. *Genes Chromosomes Cancer.* 1989; 1: 155–8.
39. **Pawson T.** Regulation and targets of receptor tyrosine kinases. *Eur J Cancer.* 2002; 38 Suppl 5: S3–10.
40. **Kitamura Y, Hirotab S.** Kit as a human oncogenic tyrosine kinase. *Cell Mol Life Sci.* 2004; 61: 2924–31.
41. **Corless CL, Fletcher JA, Heinrich MC.** Biology of gastrointestinal stromal tumors. *J Clin Oncol.* 2004; 22: 3813–25.
42. **Rubin BP, Singer S, Tsao C, *et al.*** KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res.* 2001; 61: 8118–21.
43. **Lux ML, Rubin BP, Biase TL, *et al.*** KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol.* 2000; 156: 791–5.
44. **Antonescu CR, Sommer G, Sarran L, *et al.*** Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors. *Clin Cancer Res.* 2003; 9: 3329–37.
45. **Lasota J, Wozniak A, Sarlomo-Rikala M, *et al.*** Mutations in exons 9 and 13 of KIT gene are rare events in gastrointestinal stromal tumors. A study of 200 cases. *Am J Pathol.* 2000; 157: 1091–5.
46. **Hirota S, Nishida T, Isozaki K, *et al.*** Gain-of-function mutation at the extracellular domain of KIT in gastrointestinal stromal tumours. *J Pathol.* 2001; 193: 505–10.
47. **Kinoshita K, Isozaki K, Hirota S, *et al.*** c-kit gene mutation at exon 17 or 13 is very rare in sporadic gastrointestinal stromal tumors. *J Gastroenterol Hepatol.* 2003; 18: 147–51.
48. **Lasota J, Miettinen M.** Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology*. 2008; 53: 245–66.
49. **Corless CL, Schroeder A, Griffith D, *et al.*** PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and *in vitro* sensitivity to imatinib. *J Clin Oncol.* 2005; 23: 5357–64.
50. **Hirota S, Ohashi A, Nishida T, *et al.*** Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology.* 2003; 125: 660–7.
51. **Wasag B, Debiec-Rychter M, Pauwels P, *et al.*** Differential expression of KIT/PDGFRA mutant isoforms in epithelioid and mixed variants of gastrointestinal stromal tumors depends predominantly on the tumor site. *Mod Pathol.* 2004; 17: 889–94.
52. **Debiec-Rychter M, Wasag B, Stul M, *et al.*** Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. *J Pathol.* 2004; 202: 430–8.
53. **Sakurai S, Hasegawa T, Sakuma Y, *et al.*** Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infiltrations: a subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. *Hum Pathol.* 2004; 35: 1223–30.
54. **Tzen CY, Mau BL.** Analysis of CD117-negative gastrointestinal stromal tumors. *World J Gastroenterol.* 2005; 11: 1052–5.
55. **Wardelmann E, Hrychyk A, Merkelbach-Bruse S, *et al.*** Association of platelet-derived growth factor receptor alpha mutations with gastric primary site and epithelioid or mixed cell morphology in gastrointestinal stromal tumors. *J Mol Diagn.* 2004; 6: 197–204.

56. **Duensing A, Joseph NE, Medeiros F, *et al.*** Protein Kinase C theta (PKCtheta) expression and constitutive activation in gastrointestinal stromal tumors (GISTs). *Cancer Res.* 2004; 64: 5127–31.
57. **Agaram NP, Wong GC, Guo T, *et al.*** Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. *Genes Chromosomes Cancer.* 2008; 47: 853–9.
58. **Demetri GD, Benjamin RS, Blanke CD, *et al.*** NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)–update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw.* 2007; 5: S1–29.
59. **Demetri GD, von Mehren M, Blanke CD, *et al.*** Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002; 347: 472–80.
60. **Tuveson DA, Willis NA, Jacks T, *et al.*** STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene.* 2001; 20: 5054–8.
61. **Dagher R, Cohen M, Williams G, *et al.*** Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res.* 2002; 8: 3034–8.
62. **Druker BJ, Tamura S, Buchdunger E, *et al.*** Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med.* 1996; 2: 561–6.
63. **Heinrich MC, Griffith DJ, Druker BJ, *et al.*** Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood.* 2000; 96: 925–32.
64. **van Oosterom AT, Judson I, Verweij J, *et al.*** Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet.* 2001; 358: 1421–3.
65. **Blay JY, Le Cesne A, Ray-Coquard I, *et al.*** Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol.* 2007; 25: 1107–13.
66. **Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al.*** Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med.* 2001; 344: 1052–6.
67. **Andtbacka RH, Ng CS, Scaife CL, *et al.*** Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol.* 2007; 14: 14–24.
68. **DeMatteo RP, Maki RG, Singer S, *et al.*** Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg.* 2007; 245: 347–52.
69. **Gronchi A, Fiore M, Miselli F, *et al.*** Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg.* 2007; 245: 341–6.
70. **Haller F, Detken S, Schulten HJ, *et al.*** Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumours (GISTs) with respect to imatinib resistance caused by secondary KIT mutations. *Ann Surg Oncol.* 2007; 14: 526–32.
71. **Loughrey MB, Mitchell C, Mann GB, *et al.*** Gastrointestinal stromal tumour treated with neoadjuvant imatinib. *J Clin Pathol.* 2005; 58: 779–81.
72. **Shah JN, Sun W, Seethala RR, *et al.*** Neoadjuvant therapy with imatinib mesylate for locally advanced GI stromal tumor. *Gastrointest Endosc.* 2005; 61: 625–7.
73. **von Mehren M.** The role of adjuvant and neoadjuvant therapy in gastrointestinal stromal tumors. *Curr Opin Oncol.* 2008; 20: 428–32.
74. **Nilsson B, Sjölund K, Kindblom LG, *et al.*** Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). *Br J Cancer.* 2007; 96: 1656–8.
75. **Dematteo RP, Ballman KV, Antonescu CR, *et al.*** Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2009; 373: 1097–104.
76. **Heinrich MC, Corless CL, Demetri GD, *et al.*** Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol.* 2003; 21: 4342–9.
77. **Debiec-Rychter M, Sciot R, Le Cesne A, *et al.*** KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer.* 2006; 42: 1093–103.
78. **Chen LL, Trent JC, Wu EF, *et al.*** A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res.* 2004; 64: 5913–9.
79. **Debiec-Rychter M, Cools J, Dumez H, *et al.*** Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. *Gastroenterology.* 2005; 128: 270–9.
80. **Tamborini E, Bonadiman L, Greco A, *et al.*** A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. *Gastroenterology.* 2004; 127: 294–9.
81. **Heinrich MC, Corless CL, Blanke CD, *et al.*** Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. *J Clin Oncol.* 2006; 24: 4764–74.
82. **Miselli FC, Casieri P, Negri T, *et al.*** c-Kit/PDGFRA gene status alterations possibly related to primary imatinib resistance in gastrointestinal stromal tumors. *Clin Cancer Res.* 2007; 13: 2369–77.
83. **Antonescu CR, Besmer P, Guo T, *et al.*** Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res.* 2005; 11: 4182–90.
84. **Wardelmann E, Merkelbach-Bruse S, Pauls K, *et al.*** Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. *Clin Cancer Res.* 2006; 12: 1743–9.
85. **Bauer S, Duensing A, Demetri GD, *et al.*** KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. *Oncogene.* 2007; 26: 7560–8.
86. **von Mehren M.** Beyond imatinib: second generation c-KIT inhibitors for the management of gastrointestinal stromal tumors. *Clin Colorectal Cancer.* 2006; 6 Suppl 1: S30–4.
87. **Abrams TJ, Lee LB, Murray LJ, *et al.*** SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Mol Cancer Ther.* 2003; 2: 471–8.
88. **Mendel DB, Laird AD, Xin X, *et al.*** *In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res.* 2003; 9: 327–37.
89. **Chow LQ, Eckhardt SG.** Sunitinib: from rational design to clinical efficacy. *J Clin Oncol.* 2007; 25: 884–96.
90. **Demetri GD, van Oosterom AT, Garrett CR, *et al.*** Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006; 368: 1329–38.

91. **George S.** Sunitinib, a multitargeted tyrosine kinase inhibitor, in the management of gastrointestinal stromal tumor. *Curr Oncol Rep.* 2007; 9: 323–7.
92. **Heinrich MC, Maki RG, Corless CL, *et al.*** Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol.* 2008; 26: 5352–9.
93. **Reichardt P.** Novel approaches to imatinib- and sunitinib-resistant GIST. *Curr Oncol Rep.* 2008; 10: 344–9.
94. **Montemurro M, Schöffski P, Reichardt P, *et al.*** Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. *Eur J Cancer.* 2009; 45: 2293–7.
95. **Demetri GD, Casali PG, Blay JY, *et al.*** A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. *Clin Cancer Res.* 2009; 15: 5910–6.
96. **Schittenhelm MM, Shiraga S, Schroeder A, *et al.*** Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. *Cancer Res.* 2006; 66: 473–81.
97. **Dewaele B, Wasag B, Cools J, *et al.*** Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. *Clin Cancer Res.* 2008; 14: 5749–58.
98. **Guo T, Agaram NP, Wong GC, *et al.*** Sorafenib inhibits the imatinib-resistant KITT670I gatekeeper mutation in gastrointestinal stromal tumor. *Clin Cancer Res.* 2007; 13:4874–81.
99. **Soria JC, Massard C, Magné N, *et al.*** Phase 1 dose-escalation study of oral tyrosine kinase inhibitor masitinib in advanced and/or metastatic solid cancers. *Eur J Cancer.* 2009; 45: 2333–41.
100. **Joensuu H, De Braud F, Coco P, *et al.*** Phase II, open-label study of PTK787/ ZK222584 for the treatment of metastatic gastrointestinal stromal tumors resistant to imatinib mesylate. *Ann Oncol.* 2008; 19: 173–7.
101. **Rosen LS, Kurzrock R, Mulay M, *et al.*** Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors. *J Clin Oncol.* 2007; 25: 2369–76.
102. **Stamatakos M, Douzinas E, Stefanaki C, *et al.*** Gastrointestinal stromal tumor. *World J Surg Oncol.* 2009; 7: 61.