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GASTROINTESTINAL STROMAL TUMOUR, PRESENTATION OF CASES AND OUTLINE OF THE DISEASE AND ITS MANAGEMENT

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Abstract

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract. Although GIST has been clinically recognized for almost 20 years, a standard definition has only recently been clarified. These tumours were frequently classified as leiomyomas, leiomyosarcomas, leiomyoblastomas, or gastrointestinal autonomic nerve tumours[1]. Over the past few years, scientists have begun to unravel the molecular abnormalities that underlie the pathogenesis of these tumours. They are now considered to share a common progenitor cell with the interstitial cells of Cajal[2]. GISTs are characterized by immunohistochemical expression of the CD117 antigen. Surgery is the main line of treatment in operable cases. GISTs are highly resistant to conventional chemotherapy and radiotherapy. *Imatinib*, a tyrosine kinase inhibitor is an approved specific target for systemic therapy.
The author had the chance of managing several patients diagnosed to have GISTs, recently three of them were managed during the last few months, and two more new cases are awaiting their surgery. This report is a presentation of these cases and a highlight of the clinical features, pathology, diagnosis and management of GISTs.

Introduction

A relationship of the GIST to the Interstitial Cells of Cajal (ICCs) has been proposed, and expression of CD117, the c-kit receptor present in ICC, has been considered as a marker for GISTs[2]. The interstitial cells of Cajal (a Spanish scientist) form a complex cellular network within the muscle wall of the gut where they function as a muscular pacemaker system controlling gut motility[3]. Expression of the c-kit protooncogene is essential for the slow wave activity of ICCs and for the development of the ICC system. Although not limited to this cell type, c-kit expression is widely recognized as a molecular marker of ICCs[4]. GISTs commonly have activating mutations in exon 11 (or rarely exon 9 and exon 13) of the KIT gene that encodes a tyrosine kinase receptor for the stem cell factor or mast cell growth[5].

Presentation of cases

Case One

KPP, a 61 year old male patient presented with a palpable mass in the right lower abdomen, which the patient himself felt. The mass was found to be extraperitoneal, and not tender. Approximately three years before that he was diagnosed to have prostatic cancer for which he received bracytherapy beads, and approximately two years after that the patient presented with a large palpable tumour in the lower abdomen. At that time it was investigated with CT scan and percutaneous FNAC (Fine Needle Aspiration Cytology), which showed features consistent with GIST.

Following that he underwent resection of a large (17x10x7 cm) tumour by another surgical team. The tumour was found to be related to the mesentery of the ileum. The maximal mitotic activity score of the resected GIST was 20 per 50 high power fields. According to definition set by the World Health Organisation tumours in excess of 5 per 50 high power fields are considered high grade. During the same laparotomy the appendix was found to be abnormal and therefore was removed. The histology of the appendix confirmed the presence of a carcinoid tumour of less than 18.0 mm in size. According to conventional description malignant behaviour of Carcinoid tumours is usually restricted to those of more than 20.0 mm in size. Although the GIST was of high grade, the medical oncologist thought that because it was completely removed then no further treatment was recommended. Also because the carcinoid tumour was less than 20.00 mm in size it was regarded not potentially malignant.

Before the patient was referred to us for his current problem he was investigated by his general practitioner with ultrasound and FNAC. This confirmed that the tumour lies within the abdominal wall and it is GIST. Our provisional diagnosis was a recurrence of the previously removed GIST. In order to assess his disease further and to exclude distant metastasis the patient was further investigated with CT scan of the chest, abdomen and pelvis, which showed normal findings in the chest, an 8 x 7 x 6 cm lobulated mass in the pelvis, another masses inside the abdomen and demonstrated that the palpable mass lies within the subcutaneous fat in the lower right abdomen. MRI was also performed to provide additional information about the pelvic mass, and because the patient complained from rectal bleeding a colonoscopy to the caecum was carried out which showed normal finding. The final work up diagnosis was that of recurrent widespread GISTs most likely due to the high grade nature of the original tumour resected two years previously and the occurrence of the subcutaneous tumour in the right lower abdomen was thought to be likely due to the FNAC performed at that time. We also felt that the recent FNAC, which was requested by the patient's general practitioner, was both not recommended and unnecessary.

Under general anaesthesia and epidural catheter for postoperative analgesia, the abdomen was explored. Significant adhesions were taken down, the large pelvic tumour was removed completely, in addition to removal of some 12 smaller tumours involving the peritoneum at the lower right abdomen (not previously seen by CT scan), and multiple tumours ranging in size between 1-2 cms were removed from the right paracolic gutter, loops of small bowel, large bowel mesentery, and a 2.0 cm tumour in the liver just medial to the gall bladder bed was also excised. No bowel resection was necessary. Finally the subcutaneous tumour was removed from the right lower abdomen. Several immunohistochemical studies were performed and all tumours showed positive CD 117, and mitotic figures counted up to less than 1 per 5.0 mm^2. When compared to the original tumour all new tumours were considered to be recurrent /metastatic.

The patient had an uneventful recovery and started on Imatinib 400mg daily by the medical oncologist. Follow up CT scan after three months revealed the presence of four small lesions in different segments of the liver all of them less than 2.0 cm in size, which were considered to be new metastases. However, the patient remained asymptomatic and has good quality of life.

His condition will be carefully followed.

Case Two

MPB, a 75 year old male patient presented with melaena and iron deficiency anaemia. Upper and lower gastrointestinal endoscopies didn't show any possible source of bleeding. CT Enterography showed an exophytic mass related to the small bowel loops measures 5 x 5 x 5.3 cms in size. It was inhomogeneous with a vascular blush reflect a cluster of veins, which drain into the ileocolic vein. The findings were considered to be most likely of a GIST although other possible differential diagnosis were mentioned.

Under general anaesthesia, through a few cms median incision, the mass was found to be attached and invade a loop of the mid jejunum. No gross metastatic disease was found. The mass together with the attached bowel and mesentery was resected and bowel continuity established. Pathological examination showed a 6.5 x 5.0 cms mass, hard in consistency, polypoid in texture with smooth surface arise from the muscularis portion as the mucosa looked intact. The microscopical features were consistent with GIST and the CD117 was positive. No mitotic figures were seen and therefore apart from the size there were no morphologic features which suggest aggressive behaviour. Because of these findings the patient was not offered any further treatment except of a regular follow up.

Case Three

NJM, a 75 year old female patient was investigated with abdominal ultrasound scan for recurrent left sided abdominal pain and a possible minor loss of weight. This detected a 1.6 cm solid nodule inseparable from the serosal surface of the anterior wall of the stomach, and no other abnormality seen. The differential diagnosis was that of a GIST although small serosal metastasis could not be ruled out. CT scan confirmed the same ultrasound finding. The patient then had gastroscopy to the third part of the duodenum, which showed unremarkable features apart from small sliding hiatus hernia, and a colonoscopy to the caecum revealed the presence of multiple left sided uncomplicated, diverticula. At laparoscopy no gross abnormality or pathology was seen apart from the small mass attached to the anterior surface of the stomach near the mid greater curvature. It was resected with clear margin. Pathologic examination showed the tumour to be firm and encapsulated. The mucosa was intact and the surgical margins were clear. The stomach didn't show inflammation, organism, metaplasia or dysplasia. The microscopic features were consistent of GIST and CD117 was positive. Up to 2 mitotic activities per 50 high power fields was seen, therefore the tumour was of a low grade, and because of that no further treatment was offered to the patient except a regular follow up.

Case Four

AGR a 59 year old male patient was admitted in serious condition after he sustained a very bad car accident. His wife who was sitting beside him and the lady driver of the car hit them died instantly. The patient was found to have several injuries involving the head, chest, abdomen, and limbs. He underwent several orthopaedics and general surgery operations, and stayed over a month in the Intensive Care Unit before transferring him to the general ward and eventually discharged home. The admission CT scan of the chest and abdomen showed an incidental tumour at the cardia of the stomach. It is more than 5.0 cms in size, well defined and looks expanding within the wall of the cardia. After recovery the

patient admitted to have some reflux features but no difficulty in swallowing. Before discharge from the hospital he had a repeat CT scan (some two months after the first one), which didn't show significant changes of the tumour. A gastroscopy was performed, which showed normal oesophagus, intact mucosa of the cardia and the tumour was clearly seen involving the circumferential part of the cardia. No biopsy was taken because it was felt that it will disturb the area and violate the covered mucosa, which will make it vulnerable to bleed. Also it was thought that EUS (Endoscopic Ultra Sound) is not going to add more information in this condition, and in either case the tumour needs to be completely removed. The patient is already scheduled for surgery with an attempt to resect the tumour through the abdomen, trying to keep the vagi' nerves supply of the area intact otherwise to perform a pyloromyotomy. Because the gastro-oesophageal junction is going to be disturbed then either a partial or complete fundoplication will be performed.

Case Five

CD a 65 year old male patient was referred to us by one of the Gastroenterologists. He presented with clinical features suggestive of reflux and iron deficiency anaemia. He underwent gastroscopy by the gastroenterologist, which showed the presence of sliding hiatus hernia, oesophageal ulcer and a submucosal tumour of more than 3.0 cms in size high up in the body of the stomach. Part of the mucosa covering the tumour was ulcerated. The tumour and the oesophageal ulcer were biopsied. The oesophgeal ulcer was reported to be benign due to reflux oesophagitis and the gastric tumour biopsy showed inconclusive features. Endoscopically the gastric tumour looks a GIST. The patient is awaiting CT scan to be followed by laparotomy with intent of total excision of the gastric tumour, repair of the oesophageal hiatus and total fundoplication.

Clinical features of GISTs;

Gastrointestinal stromal tumours have slight male predilection, and about 75% of patients are older than 50 years (median 60 years)[6.] . These tumours can arise anywhere in the gastrointestinal tract, most common in the stomach (50%), then the small bowel (25%), and in about 10% are in the colon and rectum, about 5% in the oesophagus and may develop within the mesentery, omentum, retroperitoneum, and pelvis in some 10% of the cases[5,7].

Generally patients with these tumours are either asymptomatic, or present with non-specific symptoms, or features related to gastrointestinal bleeding, anaemia or obstruction. Those tumours initially presenting with clinical symptoms and signs are more likely to have an aggressive course than asymptomatic, incidentally discovered tumours[6]. Although the site of origin is not a consistently reliable predictor of patient survival, gastric GISTs tend to be at lower risk for recurrence than oesophageal or small or large bowel GISTs[8].

Aggressive GISTs have a defined pattern of metastasis to the liver or throughout the abdomen, or both, and rarely metastasise to lymph nodes[6]. Extra-abdominal spread is mainly to the lungs and bone but is unusual, except in advanced cases[6,7,9].

Pathology

GISTs range in size from tiny tumours (<10 mm) discovered incidentally to very large lesions up to 350 mm (median 50 mm)[7]. They share many features that can be identified by electron microscope and immunophenotyping with interstitial cells of Cajal[10]. A popular hypothe-

sis is that GISTs either arise from the ICC, or that they share with them a common stem cell[10]. The tumours usually present as a single nodule but may be multiple. They are usually fleshy and solid but may have central cystic degeneration[10].

GISTs may be epitheloid, spindle cell, or mixed[7,10]. The tumours can be positive for KIT (95%), CD34 (60-70%), ACAT2 (smooth muscle actin; 30-40%), S100 (5%), DES (desmin; 1-2%), and keratin (1-2%). Although KIT is the most specific and sensitive marker, in about 5% it is negative. Therefore, tumours with negative KIT should be reviewed by an experienced pathologist in this field for verification[7].

Fletcher and colleagues[9] believe that almost all GISTs have malignant potential, which is supported by several retrospective reviews prior to the availability of imatinib[11]. The two factors most strongly predictive of aggressive behaviour are size >5 cm and mitotic index ≥5 per 50 high-power fields (hpfs)[9].

Mietinnen and colleagues published a revised version of the risk assessment scheme[12], based on a review of several large series. They studied several parameters, which included the mitotic index, the size of the tumour and its location. Tumours were described to have a mitotic index of ≤5 per 50 hpf or mitotic index of >5 per 50 hpf; a size of ≤2 cm, 2-5 cm, 5-10 cm or >10 cm; and compared the behaviour of tumours occurred in the stomach, duodenum, jejunum or ileum and rectum. They showed that the higher the mitotic index and the size of the tumour the higher is the risk of progressive disease, which is defined as metastasis or tumour-related death[12]. Also it appears that small bowel stromal tumours carry a higher risk of progression than gastric stromal tumours of similar size and mitotic activity[12].

Epidemiology

The incidence of GISTs is more common than was thought to be. For example in the USA it is estimated that there are as many as 4000-6000 new cases each year[11]. Stratified by risk group according to Fletcher et al criteria[9,11], the prevalence is 22.2 per million for very low risk, 51.9 per million for low risk, 24.2 per million for intermediate risk, and 22.2 per million for high risk[11].

GIST has a slight male predominance, and most patients are between 40 and 80 years at time of diagnosis, with a median age of approximately 60 years6. Nearly all GISTs are sporadic. About a dozen families with germline mutations have been reported, most of which have had a KIT mutation[13], but one carried a platelet-derived growth factor-α (PDGFRα) mutation[14]. GIST can also occur in association with the hereditary syndromes Von Recklinghausen disease (neurofibromatosis type I) and Carney triad (gastric GIST, paraganglioma, and pulmonary chondroma)[7,15].

GISTs are rare in paediatric patients and seem to fall into two subgroups: those with tumours that have a KIT or PDGFRA mutation, and those with tumours without mutations. The second group dominates, and patients are almost exclusively females with one or more gastric stromal tumours by age 20 years[16].

In few published studies and sporadic experience (personal contacts unpublished reports) it was found that GISTs coexisted with other neoplasms. Liszka et al[17] reported that in 82 patients with GISTs whom they studied 22 of them (26.8%) were diagnosed to have other neoplasms. The most common tumours were colorectal (nine cases), gastric (four cases), and pancreatic (three cases) adenocarcinomas.

They also found that there was a tendency of
more prevalence of this phenomenon in GISTs occurring in the small bowel and those with very low risk of aggressive behaviour[17]. In our first case there was a coexistent carcinoid tumour of the appendix with the original GIST.

Diagnosis

The diagnosis of GIST is often reached after laparotomy and formal pathologic examination. Approximately 70% of patients were symptomatic, 20% were asymptomatic, and 10% were detected at autopsy[18]. Tumours that caused symptoms tended to be larger with an average size of 6 cm versus 2 cm for asymptomatic tumours and 1.5 cm for those detected at autopsy. Symptoms might be vague or related to a mass effect, bleeding or obstruction[19].

CT scan and MRI often detect GISTs, which are useful to evaluate not only the primary tumour but also the liver and peritoneum. A primary tumour is typically a well-circumscribed and often highly vascular mass closely associated with the stomach or intestine. It often appears heterogeneous due to necrosis or intramural haemorrhage. Hypermetabolic uptake on Fluorodeoxyglucose (PDG) Positron Emission Tomography (PET) is highly sensitive but not specific for the diagnosis of GIST[18,19].

Endoscopy and Endoscopic Ultrasound (EUS) may be useful. GISTs are shown on radial EUS as hypoechoic mass lesions arising usually from the fourth layer (muscularis propria) or sometimes from the second layer (muscularis mucosae)[20].

Percutaneous biopsy is not recommended. Theoretically it may lead to tumour rupture and dissemination or bleeding. Furthermore, often it is difficult to make a reliable diagnosis especially if only fine-needle aspiration is performed. Core biopsies may not be unequivocal if there is necrosis or haemorrhage. However, it may be useful when the presence of another diagnosis makes a detrimental change in the management. Biopsy is also indicated in cases where the mass is marginally resectable and neoadjuvant imatinib treatment is desirable[18].

Management of localised disease

For patients with primary, localized GIST, surgery represents the only chance for cure, and extensive surgery is not usually required[7,18]. Wedge resection of the stomach or a segmental resection of the small intestine is usually sufficient. Every effort should be taken to ensure negative margins. These tumours usually displace adjacent tissues without infiltrating them and thus they can usually be lifted away from surrounding structures. Wide margins' resection has not been shown to add benefit[18]. Since GISTs rarely metastatise to lymph nodes, routine lymphadenectomy is not recommended[7]. When tumours are densely, adherent to adjacent organs, en bloc resection should be performed. Although GISTs are solid they feels soft and friable therefore caution should be taken to avoid intraoperative rupture, which increases the risk of recurrence[18]. Simple enucleation of the tumour should be avoided. Laparoscopic surgery can be used to resect small to intermediate sized tumours, especially those located in the stomach but caution is recommended in avoiding rupture of the tumour[7]. As discussed above, the prognosis following complete surgical resection is strongly affected by both tumour size and mitotic activity[9].

Complete gross resection is possible in approximately 85% of patients with primary, localized tumours[6,19]. Negative microscopic margins are achieved in 70% to 95% of these completely

resected cases6,[19]. At least 50% of patients develop tumour recurrence after complete resection of localized GIST and 5-year survival is usually about 50%[6,19].

Management of advanced disease

Definitions[21]: Locally advanced primary GIST is defined as radiologic evidence of significant involvement of a single organ with tumour size ≥5 cm or extension of the tumour to adjacent organs. Recurrent disease is defined as the presence of histologically or radiologically demonstrated recurrence of tumour after a previous surgical resection of a primary GIST. Disease appearing in the region of the previous intraperitoneal tumour is called "recurrence", and disease that had spread to noncontiguous distant sites such as the liver or lung is called "metastases"[21]. Distant metastatic disease is a disease occurring at remote structures. Regional intra-peritoneal disease is local recurrence if it involved a solitary recurrent tumour or sarcomatosis[22].

Metastasis typically presents with tumours isolated in the peritoneal cavity or the liver, or both. Historically, the median survival of patients with advanced disease was 18-24 months[6,23]. Some patients present with metastatic tumours that are technically resectable with acceptable morbidity, similar to the circumstances of our first case. However, almost all patients undergoing resection for advanced disease will develop recurrence, irrespective of the extent of the resection[6,9,23].

Before the introduction of imatinib, treatment options for patients with unresectable and / or metastatic disease were extremely limited, since these tumours have a poor response to conventional cytotoxic chemotherapy agents and radiation therapy[7]. In most cases, GIST recurrence and dissemination are intra-abdominal only and become evident by a median of 20 to 25 months after primary resection[6,19], as demonstrated in our first case. Metastases develop most frequently in the liver, the peritoneum or omentum. Extra-abdominal spread to the regional lymph nodes, lungs, bones, or subcutaneous sites is an uncommon finding[1,6,19]. The liver is the sole site of recurrence or metastasis in approximately 40% to 50% of patients[6,19].

Results of surgical management of GIST recurrence or spread have been variable, depending on such factors as the stage of disease, tumour risk profile, and length of the disease-free interval after initial resection. In their study of 200 cases with GISTs, DeMatteo et al6 analysed outcomes after first recurrence in patients who underwent complete resection of primary disease. Complete resection of a localized recurrent tumour resulted in a median survival of 54 months comparable to that after complete resection of localized primary GIST. However, median survival declined to 16 months with complete resection and to 10 months with incomplete resection of metastatic recurrent disease, and to 5 months with incomplete resection of either locally recurrent or concomitant local and metastatic recurrent disease[6].

When the clinical presentation suggest that a patient with recurrent GIST might be a candidate for surgery, comprehensive diagnostic imaging is required for preoperative staging.

There is no standard postoperative follow-up in patients who undergo surgical resection of a primary GIST. In fact, there is no proof that earlier detection of recurrent GIST improves survival. However, because there is now an effective treatment for patients with recurrent or metastatic disease, it appears reasonable to perform routine postoperative surveillance. The National Comprehensive Cancer Network (NCCN) consensus panel recommends CT scans of the abdomen and pelvis

with intravenous contrast every 3-6 months during the first 3-5 years and possibly yearly thereafter (available at URL: www.NCCN.com {accessed 17 August 2007}.

Imatinib is a small molecule tyrosine kinase inhibitor. Two important findings suggested that it might be effective against GISTs: it could inhibit the kinase activity of both wild-type and mutant KIT[24], and it inhibited the growth of a gastrointestinal stromal tumour cell line containing a KIT gene mutation[25].

Following the incident of a patient with widespread gastrointestinal stromal tumours who was given imatinib in a compassionate use protocol, the patient responded very well. Subsequent to that a multi-institutional phase I and phase II studies to treat metastatic, unresectable gastrointestinal stromal tumours with imatinib were initiated[26].

Two randomized, phase III trials to compare the efficacy of 400 mg of imatinib given either once or twice a day were done one in Europe and Australasia, and the other one in North America[27,28]. The trial designs were intentionally similar between the two trials except that the primary endpoints differed: progression free survival in the European Organisation for Research and Treatment of Cancer (EORTC) trial[27] in Australasia and: overall survival in the US National Cancer Institute (NCI) trial[28]. However, the results are very similar. Both doses of imatinib gave equivalent response rates in both trials, but it was noted that the 400 mg twice daily dose had significantly longer progression-free survival in the EORTC trial (hazard risk 0.82; 95% CI 0.69-0.98, p=0.026). A meta-analysis of the two trials, including the mutational-clinical correlation data is planned for 2007 by the Meta-GIST consortium, including study coordinators from US, NCI and EORTC GIST, and statisticians from SWOG and EORTC[7].

Imatinib reliably achieves disease control in 70-85% of patients with advanced gastrointestinal stromal tumours and the median progression-free survival is in the range of 20-24 months with a median overall survival time exceeds 36 months in all large clinical studies[27,28]. This is in a contrast to a median survival of 9 months in front-line doxorubicin-based chemotherapy[6,7,27]. Imatinib in doses of 400-800 mg/day proved to be efficacious, well tolerated, and safe. The toxicity profile is better than that of traditional chemotherapy. It was noted that 13% of patients had grade 3 or higher anaemia and 7% had neutropenia. About a third of patients had grade 2 or higher oedema, or fatigue, about a fifth had nausea or diarrhoea, and a sixth had skin rash of similar severity[29].

Adjuvant and Neoadjuvant Trials of Imatinib: Reducing local recurrences and metastases of GIST, prolonging disease-free intervals and overall survival, increasing the number of patients eligible for resection through pharmacological tumour debulking, and possibly enhancing the response to imatinib by means of surgical cytoreduction are among the potential benefits and applications that could result from data analysis in clinical studies that combine surgery and imatinib in the management of GIST[30].

Surgery and Imatinib: There is consensus as to defining profiles that can stratify patients into high risk groups who have resectable disease and may experience improved outcome with the addition of imatinib when compared to surgical resection alone[30]. Evaluation of risk based on GIST size and mitotic rate, those cases who have tumour perforation, tumour rupture during surgery, or incomplete resection supports a potential role for adjuvant imatinib administration. Patients who have un-

dergone surgery for primary GIST and return for resection of completely excisable locally recurrent or metastatic tumours may constitute another high risk group[30]. A greater understanding of the biology of GIST and how it interacts with imatinib will provide the rationale for the design of additional biologic therapeutic strategies[31].

One of the main issues arising from clinical trials is how to monitor clinical response. Standard (RECIST) criteria for evaluation of tumours, which needs a 30% reduction in tumour size to be termed a partial response[32], is clearly not appropriate because a decrease in size does not necessarily correspond with therapeutic response. Indeed, lesions can remain stable in size after therapy because of the replacement of tumour by fibrous tissue, or they might seem larger because of decreased tumour density from intratumoural oedema or haemorrhage[7,33]. Generally, tumours that respond become hypocellular with myxoid stroma and variable amounts of necrosis[7,34].

Management of imatinib-resistant tumours

In a pivotal study of imatinib in advanced GIST, 5% of patients showed primary resistance to imatinib and another 14% developed early resistance[35]. Imatinib resistance can be divided into two categories. The first group is patients who do not achieve stable disease or who progress within six months of an initial clinical response are described to have primary resistance. Tumours with a KIT exon 9 mutation or no detectable kinase mutation (wild-type tumours) are over-represented in this group[7,36]. The other group is patients who develop one or more sites of disease progression after more than six months clinical response are classified as having secondary resistance. In patients with secondary resistance, new, acquired kinase mutations are commonly seen in KIT (or PDGFRA) that interfere with imatinib activity[37]. The emergence of these secondary mutations is due to a population of tumour cells for which imatinib is cytostatic rather than cytocidal[7]. As with other cancers, medical cure of GISTs might need eradication of the transformed stem cells that give rise to the tumour[7].

Treatment of imatinib-resistant stromal tumours might involve dose escalation of imatinib, however, when this fails, patients should be assessed for possible surgical resection or radiofrequency ablation, or undergo hepatic artery chemoembolisation of liver lesions[7].

Sunitinib malate (SUTENT, previously known as SU11248; Pfizer, New York, USA) is an oral multitargeted receptor tyrosine kinase inhibitor that has shown antiangiogenic and antitumour activities in several in-vitro and in-vivo tumour models[38]. These effects can inhibit formations of KIT or PDGFRA kinase that are associated with secondary mutations[23]. In a randomized controlled, phase III trial[23], the median time to progression with sunitinib was 6.3 months versus 1.5 months with placebo. The main side effects were diarrhea, skin discolouration, mucositis, fatigue, hypertension and bleeding. There are other drugs, which have been tested but await further evaluation and safety[7].

Conclusion

The treatment and prognosis of patients with GISTs has been substantially changed by the discovery of oncogenic kinase mutations in the vast majority of these tumours, and the introduction of specific molecular therapies. However, these tumours include several different molecular subtypes that vary in their response to kinase inhibitors[7]. It is believed that these tumour conditions serve as a new framework, in which appropriate molecular classification is essential for

optimization of cancer treatment and clinical outcomes[7].

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