



Review Article

GASTRO INTESTINAL STROMAL TUMOUR : TREATMENT STRATEGIES

Masrur Akbar Khan

Abstract

Recent discoveries over the last decade have led to a greater insight to the molecular and biological behavior of GIST along with its expression of receptors like KIT and platelet derived growth factor. Consequently the advent of the tyrosine kinase inhibitor imatinib mesylate has been a phenomenal example of targeted molecular therapy. The unique success of the targeted therapy in the management of GIST has enhanced the multidisciplinary management approach to the disease. Careful and intense study of the treatment strategies in GIST may lead to new era in the management of cancer.

Key words: Gastrointestinal stromal tumour, KIT, platelet derived growth factor receptor, imatinib mesylate

Introduction

Gastrointestinal stromal tumour (GIST) is the mostly encountered mesenchymal tumour of the gastrointestinal tract. There is a new shift in the management strategy owing to the recent discovery of the KIT(CD117) proto oncogene mutation common to most GISTs that can be inhibited by imatinib mesylate. The unique and specific molecular targeting capability of imatinib has markedly enhanced the treatment of these solid tumours. However the diagnosis and treatment of GIST still requires a multidisciplinary approach that involves pathological and radiological evaluation, surgery and oncological care for better outcome of patients. It has been only a decade since GIST has been recognized as a unique and different entity. Previously thought to derive from smooth muscle cells GISTs were considered variations of leiomyosarcomas or leiomyomas. It has been leveled as different entity by immunohistochemical staining with demonstration of KIT (CD117) expression (found in 95% of GIST).¹

Epidemiology

Gastrointestinal stromal tumours (GISTs) are soft tissue sarcomas affecting the gastrointestinal tract.

Correspondence to: Medical Officer, Department of Surgery, Dhaka Medical College Hospital. email: masrur1621@yahoo.com

The estimated incidence is 14.5/1 000 000, which equates to about 5 000 new cases per year in the US.² Men and women are affected equally. While GISTs have been reported in all age groups including newborns, it is very uncommon in patients less than 30 years old.³ Peak incidence occurs in the late sixth and early seventh decades of life. Familial GISTs result from a germ line mutation in either the KIT or platelet-derived growth factor receptor alpha (PDGFR α) proto-oncogenes.⁴

Histopathology

GISTs are thought to originate from pacemaker cells of intestinal wall known as interstitial cells of Cajal (ICC) that regulate peristalsis. Nearly 95% of GISTs stain positive for KIT. Other known immunohistochemical markers for GISTs include CD34 (70%), smooth muscle actin (35%), S100 (10%), and desmin (5%).² For diagnostic purpose KIT remains the most sensitive immunohistochemical marker. There are three major histological subtypes of GIST: spindle cell (70%), epithelioid (20%), and a mixed subtype (10%).⁵

Malignancy and GIST locations

Tumour behavior of GIST can vary with a wide spectrum from benign to malignant. Malignancy is more common in intestinal GIST (40%) than gastric GIST (20%). GISTs may arise from the esophagus to the anus with commonest site being the stomach (60%). Jejunum and ileum comprises 30% of GISTs with ileal tumours being slightly less common than jejunal. GIST can also occur in the rectum, but rarely in the colon. Rarer sites include extra intestinal

organs like the gallbladder, omentum, and mesentery. Metastatic sites for GIST include the liver and omentum (most common), lungs (less common), and regional lymph nodes and bone (rare).⁶

Clinical Presentation

The clinical features of GIST are often related to its size and location. Symptoms are often due to mass effect, owing to its extraluminal location. When symptomatic clinical picture can range from vague abdominal pain to peritonitis resulting from tumour rupture and intraperitoneal bleeding. Other symptoms may include abdominal fullness, early satiety, and rarely bowel obstruction. Weakness and fatigue secondary to microcytic anemia can be the feature when tumour erodes into the intestinal lumen and cause subclinical GI bleeding. Significant haemorrhage can occur in up to 25% of patients with GIST, either caused by erosion into the GI tract or intra-peritoneal rupture.⁷

Diagnosis

High index of suspicion might point towards its diagnosis. Not surprisingly GISTs are often diagnosed only after surgical resection and pathological examination. Imaging has become the primary mode of evaluation of patients with abdominal symptoms. On MRI, GISTs show low signal intensity on T1-weighted images, high intensity on T2-weighted images, and enhance with gadolinium contrast.⁸ CT scan is the primary tool for staging of GIST. Characteristic findings on CT scan include an enhancing, exophytic mass in close association with the stomach or bowel wall. Like other sarcomas, GISTs tend to displace rather than invade adjacent structures. Endoscopic-guided fine needle aspiration has been shown to be >80% sensitive in diagnosing GIST. Endoscopic or percutaneous biopsy is controversial due to fragility of GIST with risk of tumour rupture, bleeding, and dissemination. However biopsy is indicated in selective cases to exclude the diagnosis of lymphoma which can have a similar radiologic appearance, or allow for neoadjuvant imatinib therapy for a marginally resectable tumour.

Prognosis

The critical determinants of prognosis include size of the tumour, mitotic rate, and location. Small tumours (<2cm) with low mitotic rates (<5 per 50 HPF) exhibit benign behavior, whereas larger tumours (>5cm) with high mitotic rates (>10 per 50 HPF) are associated with malignant behavior and display higher rates of recurrence after surgical resection. Stomach GISTs show less aggression than GIST in other locations. Recurrence after surgery is more common in patients with a deletion mutation in exon 11.⁹ Tumour rupture before

or during dissection carries an adverse outcome as demonstrated by high peritoneal recurrence.

Treatment

Primary Resectable Disease

Surgery has been the principal form of treatment for primary resectable GIST where complete surgical resection remains the only chance of cure. Owing to the fragile nature of GIST with widespread necrosis or hemorrhage, careful dissection is crucial to prevent tumour spillage that carries the risk of intra peritoneal recurrence. Often GISTs adhere to surrounding structures compelling additional organ resections for complete resection. To achieve microscopically negative resectional margin, a 1cm gross normal tissue is generally sufficient. A positive microscopic margin should be considered for a second look resection if possible. Laparoscopy is a suited better for small gastric GIST, since lymphadenectomy is rarely needed. Although there is a consensus regarding resection of all tumours larger than 2cm, controversy remains regarding the management of incidentally encountered small GISTs less than 2cm. Current guidelines for the management of gastric GISTs less than 2cm without high-risk features on EUS by National Comprehensive Cancer Network (NCCN) suggests endoscopic surveillance every 6–12 months.¹⁰ A standard postoperative follow up protocol following complete resections is yet to develop. Presently imatinib being available for use in treating recurrences, routine axial imaging is the cornerstone of postoperative follow up. Contrast enhanced CT scans every 3–6 months for the first 5 years, and then yearly are the current recommendations.¹² The dose of 400 mg Imatinib orally once or twice a day is well tolerated with rash, diarrhea and abdominal pain being the most commonly reported side effects. The Phase II intergroup trial (Z9000) was led by The American College of Surgeons Oncology Group (ACOSOG) in combination with Novartis and the Cancer Therapy Evaluation Program. The effect of adjuvant imatinib (400mg/day for 12 months) was assessed following complete macroscopic resection in patients with high-risk primary GIST (≥ 5 tumours, tumour size ≥ 10 cm, or intraperitoneal tumour rupture or hemorrhage). The trial demonstrated improved recurrence-free survival with imatinib (98%) and increased overall survival in comparison to historical controls (83%).¹¹ In 2009, the FDA approved imatinib for use in the adjuvant setting. In order to define the most effective length of adjuvant imatinib therapy, the results of a recently completed randomized trial comparing one year to three years of adjuvant imatinib are being finalized. It appears that overall survival is longer with 3 years versus 1 year of adjuvant imatinib.¹²

Primary unresectable GIST

There has been trials to assess the role of neoadjuvant imatinib for locally advanced disease. For unresectable or borderline GIST, the treatment of choice is imatinib. A CT scan 1 month following imatinib therapy can show the tumour response with potential resectability. When primary tumours are large and may require additional organ resection to achieve tumour free margins, imatinib is well tolerated as the neoadjuvant therapy as per the recent results from a phase II trial led by the Radiation Therapy Oncology Group (RTOG).¹³ Imatinib administered at 600mg per day for 8 weeks preoperatively. It was followed by surgical resection with adjuvant imatinib for next 2 years. This regimen had minimal toxicity with acceptable complications during perioperative period. According to current NCCN guidelines if two successive CT scans fail to show any radiographic response in patients on neoadjuvant imatinib surgery should be considered. Incomplete resections in patients with advanced disease are generally only performed in the setting of palliation for bleeding, pain, or obstruction.

Recurrent and metastatic GIST

Surgery alone has limited role in treating recurrent GIST. Imatinib is the first line of treatment in patients with recurrent and metastatic disease. CT scans or by 18FDG-PET scan can assess initial response. With imatinib a partial or complete response is observed in up to 80% of patients with metastatic GIST. Two large randomized studies compared the efficacy of imatinib 400mg given either once or twice daily. The results revealed that the higher dose confers a progression-free survival advantage. Since imatinib is not curative, combining the two modalities may delay imatinib resistance and potentially be curative. Currently at MSKCC patients are treated with imatinib for 6 months followed by surgery if complete resection is suggested on imaging. Patients are then treated with postoperative imatinib to prevent recurrence.¹⁴ For patients with advanced disease other treatment options include radiofrequency ablation (RFA), hepatic artery embolization, and liver transplantation.

Imatinib-resistant GIST

GISTs that contain mutations in exon 9 of KIT or a D842V mutation in PDGFR α , demonstrate primary resistance. Secondary resistance occurs later in the course of imatinib therapy (>6 months) results from of a second mutation in the kinase domain of KIT or PDGFR α .¹⁵ Fifty percent of the secondary mutations occur in KIT exon 17 that interfere with imatinib binding. The rest of mutations responsible for imatinib resistance can involve, activation of other kinases, increased imatinib metabolism or target gene amplification. In selective cases where one nodule continues

to grow, while the majority of metastatic disease responds to imatinib therapy, surgical resection of the resistant nodule should be considered. For patients with tumour progression on imatinib 400mg/day, the dose can be escalated to 800mg/day. Five percent of patients will respond to the escalated dose of imatinib to gain partial remission.¹⁶ Sunitinib is the second line therapy for patients who have imatinib-resistant GIST. It inhibits vascular endothelial cell growth factor receptors 1, 2, and 3, KIT, PDGFR α , PDGFR β , Fms-like tyrosine kinase-3 receptor, and the ret proto-oncogene receptor. It has been proven safe and effective in imatinib resistant cases. With significantly longer overall survival.¹⁷ Options for patients with disease refractory to imatinib and sunitinib are limited. While several third line agents such as sorafenib, nilotinib, dasatinib, and most recently vatalanib have been used in small numbers of patients, there is no clear optimal third line agent. Several other treatment modalities has also been tried, including radiation, ablation, and some novel agents. GIST are considered radiation-resistant tumour. The only role for radiation therapy is for palliative treatment or possibly with rectal GIST. The results of treatment with traditional chemotherapy have been disappointing. Specifically, <10% response have been observed by treatment with doxorubicin or gemcitabine combinations.¹⁸

Conclusion

The ultimate aim of management of patients with GIST is to enhance the scope for cure, minimize recurrence and keep the burden of metastasis low. Only then can a patient maintain an acceptable quality of life. Standard of care for treating patients with GIST involves surgical resection of primary, recurrent, and metastatic GIST along with tyrosine kinase inhibition. To optimize successful results a multidisciplinary approach is crucial.

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