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Review Article

GIST: A REVIEW

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Abstract

Non-epithelial tumours of stomach and intestine were described and termed as leomyomas because they possessed smooth muscle features when examined under light microscopy. Recently cell of origin of these tumourshave been identified as a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cells of Cajal. Gastrointestinal stromal tumours (GIST) is widely accepted term used for these tumours.

GISTs are not infrequent and can occur in any part of GI Tract and also may be extraintestinal in origin. Introduction of Imatinib, a Tyrosine Kinase Inhibitor [TKI] for treatment of GIST has made a great impact in the management options of these tumours which were refractory to majority of available cytotoxic drugs. High response rate to imatinib generated new research for newer drugs on one hand and defining genetic structure and changes in other tumours to develop more specific and successful therapy.

This review is an effort to consolidate present understanding and information about pathology diagnosis and management of GIST.

Key Words: GIST, Rhabdomyoma, Imatinib.

Introduction

Tumours of gastro-intestinal tract other than adenocarcinoma were described in early twentieth century. Historically, these lesions were classified as leiomyomas or leiomyosarcomas because they possessed smooth muscle features when examined under light microscopy. Raiford in 1931 described 3 cases of leomyoma out of 28 small intestinal tumors in a retrospective autopsy study at John Hopkins.[1] Similar observations were reported by others also. These were also known as Leiomyosarcomas or leiomyoblastomas. These were believed to arise from smooth muscles of gut wall. Mazur & Clark first introduced the term "Stromal Tumor" in 1983 to define a group of gastric mesenchymal tumors do not possess the ultrastructural and immunohistochemical features characteristic of smooth muscle differentiation, as are seen in leiomyomas.[1] With the advent of electron microscopy and immunohistochemistry, histologic criteria for the diagnosis of GIST has been determined as: A spindled and/or epitheloid mesenchymal tumor of the GIT with unequivocal KIT immunoreactivity.[2] Numerous studies have been carried out in recent years focusing mainly on molecular abnormalities, pathogenesis , diagnostic criteria & clinical therapy of GIST. The outcome is that, there are evidence based proposals regarding the diagnostic pathway, treatment plan & scheme of risk stratification of recurrence. However, information in some aspect is still lacking. This article aims to bridge this gap in knowledge & put forward all the available recommendations in a concise manner to lead the way for a future plan of management of GIST.

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Methodology

We searched Medline , PubMed and also other different websites as required to search original articles, Review articles and case reports using keywords " Gastro Intestinal Stromal Tumours", GIST, and Imatinib. Additional articles were manually searched as per referrals of key articles. Selected articles were included in the review.

Epidemiology : How common is GIST:

Epidemiological data regarding the true incidence & prevalence of GIST are meager. Lack of diagnostic pathologic criteria for GIST, previous varying nomenclature, and the finding that nearly 60% of all GIST have been diagnosed as benign tumors or tumors

of uncertain malignant potential and, thus, are not reported to national cancer registries were important contributing factors[3].

GIST comprise <1% of all GI tumors but they are the most common mesenchymal tumors of the GI tract. Mucciarini et al calculated the age-adjusted incidence rate of GIST to be 6.6/million/year in a series of 124 cases[4]. In another series of 114 cases, Tryggvason et al calculated an annual incidence rate of 1.1/100,000[5]. Nilsson et al calculated an annual incidence rate of 14.5/million & a prevalence rate of 129/million in a series of 288 cases[3]. A study based on the US Surveillance, Epidemiology & End Result(SEER) registry data from 1992 to 2000 found the age adjusted yearly incidence of GIST to be 6.8/million[6].

Who are affected by GIST:

GISTs are rare before the age of 40 years & very rare in children. They show a slight male predominance. In a series of 32 cases, Arolfo et al found the mean age of patients with GIST were 63.7 years with a range of 40-90 years & incidence was slightly higher in males(56%)[7]. In another series of 1765 cases, Miettinen, Sobin et al found that the GIST has a slight male predominance (55%) with a median age of 63 years & tumor occurrence rate of 2.7% before the age of 21 years & 9.1% before 40 years[8]. Mucciarini et al found similar results with male predominance (53.2%) & median age of presentation of 69 years (range 30-90 years)[4].

GISTs in children are a distinct subset with strong predominance for girls, multifocal gastric location, and a wild-type phenotype. Lymph node metastasis and local recurrence to the gastric stump is common in this setting. The clinical behavior of pediatric GISTs appears more indolent, compared with adult GISTs[9].

Where does GIST occur:

GISTs can occur anywhere in the Gastro Intestinal tract from the esophagus to the rectum. But the most common site is stomach as evidenced by all the large series of patients (Table I).

Approximately 10-30% GISTs are overtly malignant in behavior[9]. The principle sites of metastases are liver (65%) & peritoneal cavity (21%). Lymph node metastases are uncommon(6%). Sites of extra-abdominal metastases are bone (6%) & lungs (2%)[10].

Origin, Pathology and immunhistochemistry :

GISTs are usually circumscribed, highly vascular, soft and friable lesions. Larger tumours may ulcerate on the mucosal or serosal surface. There may be areas of necrosis or degeneration. Microscopically there are three sub-groups; Spindle cell type, Epitheloid type and mixed variety having both.

Since the term GIST was introduced by Mazur and Clark in 1983, laboratory investigations aimed at the subcellular and molecular levels have demonstrated that GISTs do not possess the ultrastructural and immunohistochemical features characteristic of smooth muscle differentiation, as are seen in leiomyomas and leiomyosarcomas. Therefore, GISTs are believed to arise from another mesenchymal derivative such as the progenitors of spindle and epithelioid cells. According to the work of Kindblom and associates reported in 1998, the actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cell of Cajal. These are GI pacemaker cells and are largely responsible for initiating and coordinating GI motility. Perhaps the most critical development that distinguished GISTs as a unique clinical entity was the discovery of c-*kit* proto-oncogene mutations in these tumors by Hirota and colleagues in 1998[5].

Table-I

Sites of GIST

Authors	Publica tion Year	Stomach	Duodenum	Jejunum & Ileum	Colon	Rectum	Intestine Unspecified	Others
Mucciarini[4] n=124	2007	62.9%			3.2%	1.6%	23.4%	8.4%
Arolfo[7] n=32	2011	56.3%				3.1%	31.3%	9.3%
deMatteo[10] n=200	2000	39%		32%	5%	10%		9%
Caterino[11] n=47	2011	59.6%	6.4%	24.4%		6.1%		4.2%
Kang[12] n=118	2010	66.1%			1.7%		28%	4.2%

Molecular diagnosis of GIST:

The increased diagnostic precision of GISTs over the last 15 years is due to widespread use of CD117 (KIT) immunohistochemistry in the routine pathologic analysis of spindle and epithelioid neoplasms of the GI tract and associated anatomic regions. Positive CD117 and/or DOG1 staining as part of an immunohistochemical panel in a spindle cell tumor of the GI tract confirms the diagnosis of GIST[5].

GISTs are heterogeneous, both from a clinical and morphologic standpoint. But regardless of their clinical diversity, they share common genetic alterations. Mutually exclusive mutations in cKIT (CD117) or PDGFRA have been identified in up to 80% & 10 % of GISTs respectively[13].

Clinical Features:

The symptoms of GISTs are nonspecific & usually depend on the size , location of the lesion and aggressiveness. They remain silent when they protrude outside the lumen until they reach a palpably large size, bleed or rupture.

Majority of patients (676 patients) presented with GI bleeding in a series of 1765 cases of GIST of stomach. This was specified as acute melaena in 150 patients and haematemesis in 44 patients, and both in 24 patients, often with insidious bleeding with anemia and weakness (89 patients). Pain and upper abdominal discomfort were the presenting symptom in 209 patients. Large asymptomatic tumors were palpated by 46 patients or their physicians and 18 patients reported abdominal fullness or increased girth. Tumor rupture caused intra-abdominal hemorrhage and acute abdomen in 21 patients. A proximal gastric tumor caused dysphagia in 7 patients, and in 5 others, a tumor in the pyloric region caused gastric outlet obstruction. In 220 patients, the tumor was incidentally detected during other abdominal surgery or medical procedure[8].

In another series of 906 cases of GIST of jejunum & ileum, GI bleeding is found to be the most common symptom-as in cases with stomach GIST. This was most often insidious bleeding with anemia and weakness. Twelve patients were known to have bleeding episodes (melaena & rarely hematemesis) severe enough to require transfusions[14].

Acute abdomen prompting emergency surgery occurred in 131 patients. This included intestinal obstruction (n = 51), tumor rupture with intra abdominal hemorrhage (n=47), and appendicitis-like acute pain (n = 33).Other clinical contexts for the discovery of tumor included evaluation of chronic abdominal pain (n=54) & pelvicmass (n=43). Symptoms such as pain, weight loss, and fever (n=22) were often associated with large and advanced tumors.

Table-II

Immunohistochemical Analysis of GIST

	Publication Year	cKIT (CD117)	PDGFRA	CD34	PKC theta	DOG-1	P16	P 27
Caterino[11] n=47	2011	100%		81%				
Kang[12] n=118	2010	89.8%	94.9%	72%	56.8%	90.7%	69.5%	44.1%
Mucciarini[4] n=124	2007	88.7%	11%					

Table-III

Clinical features of GIST

	Year *	GI Bleeding	Abd Pain	Palpable Lump	Acute Abdomen	Asymp-tomatic	Others
Caterino [11]n=47	2011	30%	38%	10.6%	10.6%	19.1%	
Arolfo[7]n=32	2011	50%	37.5%			6.3%	6.2%
Mucciarini[4]n=124	2007	25%	35.5%	8.1%			31.4%

* Publication Year

Diagnostic tools:

In the majority of cases, a definitive diagnosis of GIST is made only after surgery. For inoperable or metastatic tumors biopsies should be taken, endoscopically to allow definitive treatment. Laparoscopic biopsies may be considered if a biopsy cannot be done by other means, but in general should be avoided due to the risk of precipitating acute abdominal events. Percutaneous biopsy is not recommended because of the potential risk of peritoneal seeding or tumor rupture. The pathologist's report should include: Tumor site, Mitotic index, Tumor size and risk of recurrence.

Preoperative diagnostic evaluation of gastrointestinal stromal tumors is based on imaging techniques, with a special role of endoscopic examination, because it is commonly accessible. However the most important diagnostic tools are the histological and immunohistochemical examinations.

Role of Imaging Studies:

Barium studies: Contrast studies using barium show the classic features of submucosal masses of the GI tract.[15] GISTs are often missed on conventional testing such as endoscopy and biopsy because of their extramural growth.

Ultrasonography: Trans-abdominal ultrasonography helps to characterize the internal echotexture of both primary and metastatic GIST; this can define whether the lesion has undergone cystic necrosis either as a result of imatinib therapy or as part of the natural history of the disease. EUS is a valuable imaging technique for diagnosing small (<2 cm) incidental GISTs & is most useful in the esophagus, stomach, duodenum, and the ano-rectum. The high frequencies used in EUS can delineate the gut wall layers and hence the layer of origin of a submucosal mass can be defined.[15]

Computed Tomography: Use of CT is 3 folds:

- **Detection of tumor**: Small tumors appear as sharply margined, smooth-walled, homogeneous, soft tissue masses with moderate contrast enhancement. Large tumors tend to have mucosal ulceration, central necrosis and cavitation, and heterogeneous enhancement following IV contrast. Organ of origin can be defined by multiplanar reconstruction[15].
- **Detection of metastases**: CT of chest, abdomen and pelvis is recommended for staging of GIST, with the exception of small incidental tumors.
- **Detection of recurrence**:Contrast-enhanced CT scan plays an important role in early detection of tumor recurrence or progression. After treatment, tumors become hypodense and their sizes decreases & stabilize. Recurrence or disease progression is diagnosed by finding an increase in tumor size, the development of new lesions at the site of previous disease or by finding distant metastasis[16-18].

Magnetic Resonance Imaging: It is an alternative option and is indicated for surgical planning in rectal GISTs, for evaluation of liver lesions indeterminate on CT scan, and for cases in which CT scan is contraindicated. On MRI, GISTs are generally well defined; the solid portions of the masses are typically of low- to intermediate- signal intensity on T1-weighted images and high signal intensity on T2-weighted images[19-22].

Positron Emission Tomography: the value of PET is two-fold. Most GISTs appear to take up ^{18}FDG avidly and thus PET represents a very sensitive staging tool, capable of demonstrating the presence of metastatic disease that is not visible on CT. Secondly, if the patient has metastatic disease with a positive PET scan, and is going to receive treatment with imatinib, then PET will provide a rapid means of determining the responsiveness of the tumor to imatinib, showing response much earlier than response can be seen on CT.The disadvantages are that it is not widely available & may not detect tumors <2 cm diameter[23].

Positron Emission Tomography – Computed Tomography (PET-CT): By combining the functions of standard PET scanners with those of CT scanners, PET-CT scanners have been shown to display more metastases from GISTs than CT and PET alone. Antoch et al. found that in 20 patients with GISTs, PET-CT demonstrated 282 lesions, whereas 249 were detected by CT alone and 135 by PET alone.PET-CTalso shows improved accuracy in the characterization of imatinib response[24,25].

Differential Diagnosis:

It is important to differentiate between GISTs, which constitute approximately 80% of GI mesenchymal tumors, and the less common GI non-epithelial neoplasms, leiomyoma, leiomyosarcoma (10-15% of

mesenchymal tumors), schwannomas (5%), and other malignant disorders[26].

Prediction of Tumor Behavior:

Unlike other GI malignancies, the behavior of GIST is difficult to predict based on histopathology alone. Many factors including tumor size, mitotic rate, tumor location, kinase mutational status and occurrence of tumor rupture have been proposed to be predictors of survival outcomes, but tumor size and mitotic rate are the two most widely accepted indices.

In 2001, the National Institutes of Health (NIH) in the USA developed by consensus scheme for predicting the risk of recurrence or metastasis of a surgically resected primary GIST (Table-V).

Table-V

Proposed Approach for Defining Risk of Aggressive Behavior in Gastrointestinal Stromal Tumors (NIH-Fletcher) [2]

Risk Stratification	Size of lesion	Mitotic Index
Very low risk	<2cm	<5/50 HPF
Low Risk	2-5cm	<5/50 HPF
Intermediate risk	<5cm	6-10/50HPF
	5-10 cm	<5/50 HPF
High Risk	>5cm>	>5/50HPF
	10cm	any mitotic rate
	any size	>10/50 HPF

The US AFIP prognostic criteria developed on the basis of a meticulous assessment of two large series of patients followed up for a median of about 15 years account for tumor site and provide more detailed risk stratification. They proposed guidelines that incorporated anatomic location, separating the classical risk factors of tumor size and mitotic count between gastric and small intestinal origin.

Memorial Sloan-Kettering cancer center (MSKCC) sarcoma team developed a nomogram to estimate the probability of recurrence-free survival based on tumor size (a continuous variable), location (stomach, small intestine, colon/ rectum, or other), and mitotic index (<5 or > or =5 per 50 HPF) after surgery for 127 patients with primary GIST at MSKCC. The nomogram was tested in the Spanish Group for Research on Sarcomas (GEIS) which consisted of 212 patients and in the Mayo Clinic (Rochester, MN, USA) group which consisted of 148 patients. Risk scores associated with each factor are first added up; then, the predicted probability of 2-year and 5-year recurrence-free survival can be read from the nomogram. This nomogram showed a better predictive accuracy than the NIH-Fletcher staging system and also the AFIP-Miettinen staging system. [28]

Treatment:

Treatment options for GIST vary based on the size & location of the tumor, presence of metastatic deposits & resectability. These treatment options have been changed over last few years-specifically with the use of tyrosine kinase inhibitor IMATINIB (formerly known as STI-571). In 2001, a remarkable case report published in the NEJM described a single patient with metastatic GIST, treated with imatinib mesylate, a tyrosine kinase inhibitor previously approved for the

Table-VI

Risk of progressive disease (AFIP-Miettinen)[27]

MitoticIndex	Size	Gastric	Jejunal/Ileal	Duodenal	Rectal
≤5/50HPF	≤2cm	0%	0%	0%	0 %
	>2cm to ≤5cm	1.9%	4.3%	8.3%	8.5%
	>5 cm to d"10 cm	3.6%	24%	34%	57%
	> 10 cm	12%	52%	34%	57%
>5/50HPF	≤2cm	0%	50%	Insufficient data	54%
	>2cm to ≤5cm	16%	73%	50%	52%
	>5 cm to ≤10 cm	55%	85%	86%	71%
	> 10 cm	85%	90%	86%	71%
Key	No Risk	Very Low Risk	Low Risk	Moderate Risk	High Risk

treatment of chronic myelogenous leukemia (CML). The response was dramatic and started a new era. Previously patients with a ruptured tumor or multifocal peritoneal nodules at the time of resection of primary tumor have been treated with several conventional adjuvant chemotherapy without demonstrable benefit. However, a number of significant clinical issues remain. These include optimal disease risk stratification, length of adjuvant treatment, optimal imatinib dose and timing of surgery.

Primary Disease:

Surgery:

Surgical resection has been the mainstay of therapy for GIST from pre Imatinib era. The primary goal of surgery is complete resection of disease without tumor rupture aiming for a macroscopically complete resection with negative microscopic margins. Unlike intestinal adenocarcinomas, GIST rarely metastasizes to lymph nodes, and thus lymphadenectomy is seldom warranted. Achieving negative pathologic margins of resection is not difficult because GIST tend to hang from, not diffusely infiltrate, the organ of origin. Consequently wedge resection of the stomach or segmental resection of the intestine provides adequate therapy and wide resection has no known benefit[29 -32]. An adequate cancer margin is considered to be 2 cm but this is not always possible. The surgeon should aim to preserve function, but not at the expense of R_0 resection. In cases where adjacent organs are involved, en bloc resection is recommended whenever possible[33,34]. Extensive surgery is occasionally required for large or poorly located tumors, such as those near the gastro esophageal junction, peri ampullary region, or lower rectum. These tumors should also be carefully handled to avoid tumor rupture, which leads to a very high risk of intra-abdominal dissemination and recurrence[35]. The 5- year overall survival rate after complete resection of GISTs is 50%- 65%[10,31,32].

Adjuvant therapy: The outcome of surgery alone has not been very satisfactory. In a recent analysis of 200 patients with GIST treated and followed prospectively at the Memorial Sloan-Kettering Cancer Center (MSKCC), 80 patients with primary tumor without metastasis underwent complete gross surgical resection, and their 5-year disease-specific survival rate was 54%. At a median follow up of 24 months, 32 of these 80 patients (40%) developed recurrent disease. Patients with tumors >10 cm had a disease-specific 5-year survival of only 20% after resection.[10] Investigators at the M.D. Anderson Cancer Center (MDACC) have reported similar results with 60% of 122 patients presenting with recurrent disease within 2 years of primary tumor resection. [36] The early results suggest that Imatinib increases recurrence-free survival and may be an effective treatment to prevent recurrence following primary surgery.

The American College of Surgeons Oncology Group (ACOSOG) Inter- group Adjuvant GIST Study Team undertook a randomized phase III, double-blind, placebo-controlled, multicenter trial (Z 9001), the aim of which was to assess the effectiveness of Imatinib as adjuvant therapy in patients who had undergone complete resection of primary GIST. In total, 708 patients who underwent complete gross resection of a primary GIST of at least 3 cm in size and expressing KIT were randomized in a double blind fashion to 1 year of Imatinib at 400 mg/day (n=359) or placebo (n=354). At a median follow-up of 19.7 months, 30 (8%) patients in the imatinib group and 70 (20%) in the placebo group had tumor recurrence or had died. Imatinib significantly improved recurrence-free survival compared with placebo (98% vs. 83% at 1 year)[37]. Based on these results, in 2008, imatinib was approved at a daily dose of 400 mg by the U.S. Food and Drug Administration (FDA) as adjuvant therapy for high-risk patients following complete surgical resection of GIST. In 2009, the European Medicines Agency approved the use of adjuvant imatinib for the same group of patients. Nevertheless, controversy over the duration of therapy remains.

Neoadjuvant therapy:

More than half of the new cases of GIST present with advanced or metastatic disease at diagnosis. Strategies that combine the use of imatinib and surgical resection have been tried as the mainstay of treatment for advanced GISTs. Neo-adjuvant therapy is given to improve on the results of surgery. In many patients with large or poorly localized primary tumors that would require extensive surgery or sacrifice a large amount of normal tissue, neo adjuvant imatinib can lead to reduction in tumor size making surgical resection to be safer and to have a better chance of getting a negative margin.

A nonrandomized Phase II trial testing neo-adjuvant / adjuvant imatinib for primary advanced and potentially operable metastatic / recurrent GIST was carried out

by the Radiation Therapy Oncology Group (RTOG). In this study the patients with primary GIST (e"5 cm, group A) or resectable metastatic / recurrent GIST (e"2 cm, group B) received neo-adjuvant imatinib (600 mg/day) for approximately 2 months and maintenance postoperative imatinib (600 mg/day) for 2 years. Sixty-three patients were originally enrolled (53 analyzable: 31 in group A and 22 in group B). Estimated 5-year progression-free survival and overall survival were 57% in group A, 30% in group B; and 77% in group A, 68% in group B, respectively[38]. Current recommendation is use of preoperative target therapy on a case-by-case basis at centers with experience in the treatment of GIST.

Treatment for locally advanced inoperable disease, metastatic disease and recurrent disease: Imatinib has been used as a neo adjuvant therapy for down staging a tumor which can later pave the way for surgical resection or as the only available option for locally advanced inoperable disease or metastatic disease or recurrent disease.

Surgery: Since there is no clear evidence of benefit from initial de-bulking surgery, it is not recommended unless there is an immediate clinical need, such as to remove an obstruction or to stop bleeding[39]. However. Surgery is recommended following maximal tumor response, generally after 3-6 months of neo-adjuvant.

Preoperative tumor downstaging therapy:

There are several prerequisites for a successful neoadjuvant therapy or tumor down staging and salvage surgery treatment regimen: - 1. An effective treatment, which can shrink the tumor in a significant proportion of patients; 2. A close radiological monitor on the tumor response to the treatment and 3. Repeated assessment by surgeon with a view to carry out curative resection at the right time. Several series reported the experience with preoperative down staging therapy with imatinib at various medical centers[40,41,42]. Imatinib is the preferred initial treatment for patients with locally advanced unresectable disease. One clear message is that salvage surgery following tumor down staging gives good survival outcome and the possibility of a cure in a proportion of patients with unresectable GIST.

Imatinib: Imatinib was tried in an open label, randomized, multicenter trial. One hundred and forty-seven pre-treated patients (98% prior surgery, 51% prior chemotherapy, and 15% prior radiation therapy) were randomized to receive imatinib 400 mg or 600 mg orally taken once daily. The primary aim was to evaluate the objective response rate of GISTs to imatinib, and the secondary aim was to assess the safety, tolerability, pharmacokinetics, time to treatment failure, and survival. CT or MRI evaluated tumor response. All complete response (CR) or partial responses (PR) were confirmed 4–12 weeks later by a second assessment.[18] FDG-PET scanning was performed to assess possible changes in the metabolic profile of the tumors and in order to compare this imaging technique with standard CT imaging. Analysis of data collected for up to 34 months showed that 84% of patients derived clinical benefit from imatinib therapy, maintaining CR (1%) or PR (67%) or stable disease (SD; 16%). Imatinib was well tolerated with a low incidence of severe side effects. The 600 mg dose was not significantly more toxic than the 400 mg dose. Following the initiation of imatinib therapy, 80% of the patients (20/25) demonstrated a metabolic response based on evaluation of the PET images. A metabolic response could be observed as early as 24 hours following the administration of a single dose of imatinib. Median time to onset of a CR or PR was 13 weeks[43]. The long-term results of this study showed an almost identical response rates, median progression-free survival and median overall survival in both treatment arms. The median survival was 57 months for all patients. Nearly 50% of patients with advanced GIST treated with imatinib survived for more than 5 years regardless of 400 or 600 mg daily starting dose[44].

The EORTC performed a dose escalation study over the range of 400 to 1000 mg daily. This established 800 mg daily as the maximum tolerated dose[45]. Phase III trials performed both in Europe and Australasia (EORTC 62005 study by EORTC & AGITG)[46]. and in North America (S0033 Intergroup study)[47]. compared imatinib at doses of 400 mg and 800 mg. Apart from confirming the efficacy of imatinib in a larger patient population, a progression-free survival for the 800 mg dose was reported in the larger EORTC study[46]. The improved response and progression-free survival seen in the North American study was not statistically significant[47]. However, a meta-analysis of the combined dataset of 1640 patients has proven that patients with *KIT* exon 9 mutations have a better outcome if treated at 800 mg daily[48]. Both the phase III trials reported that a proportion of patients progressing on imatinib 400 mg daily, who were allowed to crossover to 800 mg daily, experienced

response or disease stabilization. In the EORTC study, approximately 30% of patients were still on treatment at 12 months after crossover.[49] Based on these studies, two groups were found to be benefited from the treatment with 400 mg twice daily of imatinib: (1) patients with disease progression on standard-dose therapy, and (2) patients whose tumor harbors an exon 9 mutation in KIT.

The duration of imatinib therapy in advanced GIST has been evaluated in two French Sarcoma Group Phase III randomized studies separately evaluating outcomes of patients with responding or stable disease to interruption of treatment after 1 year and after 3 years of imatinib, respectively[50.51] No differences in overall survival or imatinib resistance were observed between the two arms[50]. In another study, 50 patients with non-progressive disease who had received 3 years of treatment with imatinib were randomly assigned. After a median follow-up of 35 months, 2-year progression-free survival was 80% in the continuation group and 16% in the interruption group[51].

Imatinib is an effective treatment for unresectable and/or metastatic GISTs that affect the natural history (time to progression) of the disease. In addition, imatinib increases survival in patients with metastatic and/or unresectable GISTs, in comparison with historical treatment. Imatinib treatment is usually continued indefinitely in the absence of disease progression or unacceptable toxicity, since treatment interruption is generally followed by relatively rapid tumor progression in virtually all patients.

The newer agents

Progression of disease on first line therapy with Imatinib is caused either by initial resistance or more often a secondary mutation in tyrosine kinase KIT or PDGFRA. The standard approach in the case of tumor progression on 400 mg once per day is to increase the imatinib dose to 400 mg twice per day as permitted by toxicity. Around one-third of patients with unresectable and/or metastatic GIST, who fail on 400 mg per day of imatinib, show response or have stable disease with the escalated doses[53, 54]. Those who have progressive diseases, or are intolerant of imatinib, are treated with a second-line tyrosine kinase inhibitor, Sunitinib malate at a dose of 50 mg per day in a 4-weeks-on/2-weeks-off regimen. Demetri and colleagues published their double-blind randomized, phase III trial comparing Sunitinib in 207 patients and placebo in 105 patients who had advanced GIST resistant to or intolerant of previous treatment with

Table-VII

Overview of Imatinib clinical studies in GISTs

	Phase & Design	Imatinib dosing schedule	No of patients	Median Age (yrs) (Range)	Response Rate	Overall Survival
EORTC 62001[45]	I	400-1000mg	40 (35 with GIST)	53(29-69)	PR=54%	Median not reported
EORTC 62001[52]	II	800 mg od	27 GIST	53	CR=4% PR=67% SD=18%	Median not reported
Novartis Registration Trial[43]	II R, O, M	400 mg od 600 mg od	147	54	Overall: CR=1% PR=67% SD=16%	57 months
Intergroup centers[47]	III R, O, M	Comparison between 400 mg & 800 mg od	746	61 (17-94)	400 mg od CR=5% PR=40% SD=25% median survival was 55 months	800 mg od CR=3% PR=42% SD=22% median survival was 51 months

Imatinib. The median time to tumor progression was 27.3 weeks in patients receiving Sunitinib and 6.4 weeks in those on placebo[55]. A phase II study evaluated whether continuous daily dosing at a lower dose of 37.5 mg per day would be potentially as efficacious and less toxic than the 4/2 schedule. The overall clinical benefit rate was 53% (13% experienced partial responses and 40% stable disease). The median progression-free survival was 34 weeks and the median overall survival at the time of analysis was 107 weeks[56]. No new adverse events were apparent compared with the approved intermittent dosing schedule. The results of this study suggest that continuous daily dosing appears to be an effective alternative dosing strategy with acceptable safety for patients. In 2006, the FDA approved second-line use of Sunitinib in patients with advanced GIST who fail (or are intolerant of) imatinib therapy.

Other tyrosine kinase inhibitors have been explored as potential treatments for metastatic or unresectable GIST. These include nilotinib and masatinib.

Nilotinib was recently evaluated in a phase I clinical trial for efficacy[57]. In this trial, 53 patients who had failed prior tyrosine kinase therapies (either imatinib or sunitinib) were randomized to receive nilotinib alone at 400 mg twice a day, nilotinib at 400 mg once a day with imatinib 400 mg twice a day, nilotinib 400 mg twice a day and imatinib 400 mg twice a day, or nilotinib 400 mg twice a day and imatinib 400 mg once a day. The investigators concluded that nilotinib, either in combination with imatinib or alone, were an effective treatment for GIST.

Currently clinical trials on newer drugs Nilotinib, Masitinib, Olaratumab, Regorafenib, Dasatinib, Dovitinib, Pazopanib (Votrient), Pazopanib, Crenolanib, Linsitinib are being conducted at different centers.[58]

Comprehensive understanding of GIST has been possible with the advent of electron microscopy & immunohistochemistry. The advancement of diagnostic capability of GIST and our understanding of it's pathogenesis enabled the development of risk - prognostic scoring. Evidently developing influencing treatment strategies has shown success. Imatinib and newer tyrosin kinase inhibitors ensured better response to surgical and adjuvant treatment. The future goal should be to translate laboratory successes into biologically relevant therapeutics, integrating the molecular therapy well with surgery, for the management of operable or inoperable GIST. Large multi-institutional clinical trials are already under way not only to discover newer agents for the Imatinib resistant GISTs, but also to evaluate the effectiveness of Imatinib in an adjuvant or neoadjuvant setting.

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