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RESEARCH ARTICLE

GASTROINTESTINAL STROMAL TUMORS: THREE DECADES OF LESSONS

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ABSTRACT

Gastrointestinal stromal tumors have been a diagnostic dilemma to the medical science in the past decades because of the clinical presentation and improper classification. These tumors generally arise in the gastrointestinal tract especially the stomach, however extraintestinal GISTs are not uncommon. The clinical presentation may vary from an indolent to aggressive course depending upon the tumor size, site of involvement, and mitotic figures. The advancements in histopathology, imaging techniques and molecular diagnostics allowed us to know the nature, mutations and biologic behavior of these tumors. Activating mutations of *cKIT*, *PDGFRA* or some other downstream key molecules endows the cells of Cajal with the capacity to grow as GIST. These mutant cells are amenable to newer therapeutic regimen, like imatinib mesylate that inhibits activation of the KIT and PDGFα proteins by binding to the adenosine triphosphate binding pocket required for receptor phosphorylation and activation. Apart from drug therapy, surgery is still the only potential curative treatment, if the tumor is amenable to it. Combinations of newer diagnostic techniques, surgical methods, and adjuvant or neoadjuvant therapies have opened doors to treat these cases in a far more efficient way.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the abdomen, with annual incidences between 11 to 20 million. These tumors most commonly involves the alimentary canal.[1-3] In the past, these tumors were classified as leiomyomas, leiomyosarcomas, or leiomyoblastomas. With the advent of immunohistochemistry and electron microscopy, GIST is recognized as a separate entity.[4-9] The term "stromal tumor" was first described as a separate entity by Mazur and Clark[10] in 1983 and Schaldenbrand and Appleman in 1984.[11]

The immunohistochemistry helped in deciphering the origin of these tumors as a large proportion of these tumors found reactive for CD34, a marker related to interstitial cells of Cajal.[12-14] It was in 1998, when Japanese researchers discovered a specific mutation in intracellular domain of *cKIT* proto-oncogene in these tumors. About 40% to 70% cases of GIST usually arise in the stomach, 20- 40% in the small intestine, and less than 10% in the esophagus, colon, and rectum.[15-17] GISTs can develop outside the intestinal tract, within the abdominopelvic cavity such as the omentum, mesentery, uterus, and the retroperitoneum; they are called extra gastrointestinal stromal tumors (eGIST), usually behaving aggressively.[16,18-20]

Epidemiology

The actual incidence of the GIST is not easy to determine as the medical science came to know its existence in the recent past only. GISTs are categorized as a separate entity in late 90s. Furthermore many of these smaller tumors grow insidiously and are identified only at the time of autopsy or gastrectomy performed for other causes.[21] The incidence of GIST is estimated to be approximately 10-20 per million people, per year. Malignancy possibility is 20-30%.[6,22,23] In the United States, GIST has an estimated annual incidence of approximately 3,000-4,000, making it the most common primary mesenchymal tumors of the gastrointestinal tract.[18,24] A few studies done to estimate the burden of

GIST indicate the incidences of approximately 14.5 cases/million/year in Sweden,[4] 14.2 in Northern Italy,[25] 13.7 in Taiwan,[5] 12.7 in Holland,[23] 11 in Iceland,[6] and 6.5 in Norway.[26] In a recent report published in 2011, about 5,000 new cases of GISTs were diagnosed annually.[27]

GISTs commonly affect adults beyond 40 years with a median age of 63 years, but no age is spared. These tumors have been reported in all ages, including children.[22] There is no clear gender preference but some studies show slight male predilection.[25,28] The true incidence in children is not known and this tumor is considered as a rare pediatric neoplasm, which is quite different in its presentation from that of adults and seen predominantly in second decade with a slight female predilection.[29-31] There is no data proving that GISTs have any geographic ethnicity, racial, or occupational predilection.

Though the majority of GISTs appear to arise sporadically, a number of families with high frequencies of GISTs have been reported having a germline mutation. The first germ line mutation found was containing a mutation in exon 11 of cKIT.[32,33]

Pathogenesis

The majority of GISTs (85%) harbor a mutation in cKIT, which leads to gain of function and continuous activation of KIT and its receptor tyrosine kinase (also known as CD117).[34] Which can be demonstrated by immunohistochemical examination in 70-80% of GISTs. This CD117 positivity provided us an excellent opportunity to diagnose these cases and mutant receptor tyrosine kinase has opened doors for specific targeted therapy using imatinib to treat such cases. KIT is a 145 kD transmembrane receptor tyrosine kinase for stem cell factor. The binding of growth factor to KIT results in homodimerization and activation of tyrosine kinase and concomitant activation of downstream intracellular signal transduction pathways, most notably RAS-RAF-MAPK and P13K-AKT-mTOR pathways.[35] The gain of function mutation in *KIT* endows cell with capacity to change its cellular functions, which includes adhesion, migration, differentiation, and most notably cellular proliferation with a decrease in cellular apoptosis. All these changes may culminate in neoplasia.[18]

Not all GISTs carry cKIT mutation, approximately one quarter of these cases have alterations of other signal transducing pathways. A different morphologic type of GIST, epithelioid appearing GIST of the stomach carry a mutations in platelet derived growth factor receptor α (PDGFRA)**.**[36,37] GISTs with PDGFRA mutation have an indolent clinical course and show variable expression of CD117.[38,39]

There are some GISTs labelled as wild-type, which do not carry either KIT or PDGFRA mutations. These tumors have poor prognosis as they respond poorly to imatinib therapy. Recent studies suggest that these tumors carry insulin like growth factor 1 receptor (IGF1R) mutation and present in both adult and pediatric wild-type GISTs.[18,40]

Clinical Presentation

Only two-third of the patients having GISTs are symptomatic, while 20% are asymptomatic and 10% are detected at autopsy.[22,37] GISTs remain asymptomatic until they reach a size of at least 6 cm in diameter.[41] Small tumors (<2 cm) are commonly incidental diagnosis, found during endoscopy, imaging or laparoscopy/laparotomy done for other reasons. Larger GISTs may present as a palpable intra-abdominal mass. Symptoms are generally nonspecific and vary according to tumor size and location. Symptoms include abdominal pain, nausea, dyspepsia, and mucosal ulceration with chronic to overt bleeding, anorexia, weight loss, fatigue, fever and intestinal obstruction. On rare occasions, rupture of the tumor may cause life threatening intra-abdominal bleeding.[42,43]

Malignant GISTs comprise of approximately 20-25% of gastric and 40-50% of small intestinal GISTs. They commonly metastasize to abdominal cavity, liver and rarely bones and soft tissue. Furthermore, lymphnodes and skin are very infrequent sites for metastasis.[44,45] Intra-abdominal GISTs have high propensity to seed the peritoneal cavity, whereas hematogenous route is preferred for liver metastasis.[46]

The majority of GISTs are sporadic but about 5% of GISTs can be either familial (familial GISTs) or associated with any of these syndromes, neurofibromatosis type 1 (NF1), Carney's triad (CT), and recently, the Carney-Stratakis triad (CSS).[16,47–49]

Familial GIST syndrome (FGS) usually presents with multiple GIST in the small bowel and less commonly in the stomach. GISTs associated with FGS have also been described in esophagus and rectum. Histomorphologically, these tumors are similar to sporadic GISTs but mitotically less active. These GISTs express CD117/KIT, as well as CD34 in immunohistochemical staining. Clinically, hyperpigmentation, increase in the number of nevi, urticaria pigmentosa, and/or systemic mastocytosis can be present.[16,47]

Approximately 7% cases of neurofibromatosis type I (NF1) harbor multiple GISTs. The most characteristic findings of NF-1 include café au lait spots, axillary and inguinal freckling, multiple dermal neurofibromas, and Lisch nodules. Although gastrointestinal manifestations of NF-1 are less frequent than cutaneous manifestation, it is not uncommon. These symptoms include hyperplastic lesion of intestinal neural tissue, GISTs, endocrine cell tumor of the duodenum, and the periampullary region, as well as other miscellaneous groups of tumors.[50] NF-1-related GISTs are usually multiple, occurring in the small bowel, predominantly show a spindle-shaped morphology, and do not harbor either *KIT* or *PDGFRA* mutations, although it can express KIT in immunohistochemical staining.[16]

The Carney triad (CT) and the more recent Carney-Stratakis syndrome (CSS) are the two other syndromes that predispose to GISTs. CT generally presents in younger females (<30 year), presenting with a combination of multiple gastric GIST, paraganglioma, and pulmonary chondroma. These lesions carry higher risks of metastasis, particularly to the lymph nodes. They are morphologically different from sporadic GISTs. No germ-line mutation specific for CT has been discovered to date. Neither *KIT* nor *PDGFRA* proto-oncogene has been found on analysis of these patients. CSS affects younger individuals more than CT. Both males and females are equally affected. CSS-related GISTs tend to be multiple, localized in the stomach, with an epithelioid morphology. Clinically, these patients present with multifocal GISTs, paragangliomas, and pheochromocytomas. Carney Stratakis syndrome exhibits a germline mutation in succinate dehydrogenase enzyme (SDH).[16,47-49,51]

Diagnosis

Diagnosis is generally delayed because of vague presentation of these tumors and many of these tumors don't cause any symptom at all. The initial workup includes an endoscopic examination as most of the tumors arise from upper gastrointestinal tract. Endoscopic ultrasonography (EUS) is helpful in diagnosing these tumors as it is accurate and efficient for this purpose.[52] Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) has shown its efficacy in many studies and can be considered as a diagnostic tool of choice in managing GISTs.[53-55]

Contrast enhanced computed tomography (CECT) gives better results in assessing the exact tumor size, extension, and metastasis, if there is any. On CECT, GISTs generally appear as a well-defined mass of soft tissue with heterogeneous enhancement.[53] The larger GISTs show more heterogeneous enhancement because of necrosis, hemorrhage and myxoid degeneration. Other imaging technique, like magnetic resonance imaging (MRI) can be helpful prior to a planned surgery of rectal GISTs and to assess metastatic lesions, which are indeterminate on CT scan.[56-59]

Constitutionally active tyrosine kinase makes these tumors glucose hungry, and it allows us to retrieve useful information about tiny lesions, tumor activity and response to therapy by using ^{18}fluoro-deoxyglucose-positron emission tomography (^{18}FDG-PET).[60,61]

Small GISTs often form solid sub-serosal, intramural, or less commonly polypoid intraluminal masses. A majority of larger GISTs form external, sometimes pedunculated masses attached to outer aspect of gut involving the muscular layers.[62] The most common of all, gastric GISTs are grey-white and well circumscribed tumors. The cut surface is generally tan-white to fleshy pink. Larger GISTs may show areas of necrosis, hemorrhage, and central area of cystic degeneration.[29]

Histologically, GISTs show three different morphologic patterns; spindle cell type, epithelioid cell type and a third type, which has a mixed population of both spindle and epithelioid cells. GISTs show a wide range of cellularity, hypocellular to highly cellular. However anaplastic features like nuclear pleomorphism are uncommon. Spindle cell GIST is the most common type and accounts for about 70% of all GISTs.[63,64,65]

Table 1 TNM staging for gastrointestinal stromal tumors (GIST)

Primary tumor (T)				
TX	Primary tumor cannot be assessed			
T0	No evidence for primary tumor			
T1	Tumor 2 cm or less			
T2	Tumor more than 2 cm but not more than 5 cm			
T3	Tumor more than 5 cm but not more than 10 cm			
T4	Tumor more than 10 cm in greatest dimension			
Regional lymphnodes (N)				
N0	No regional lymph node metastasis*			
N1	Regional lymph node metastasis			
Distant metastasis (M)				
M0	No distant metastasis			
M1	Distant metastasis			
Histologic grade (G)¶				
GX	Grade cannot be assessed			
G1	Low grade; mitotic rate ≤5/50 HPF			
G2	High grade; mitotic rate >5/50 HPF			
Anatomic stage/ prognostic groups				
Stage	**T**	**N**	**M**	**Mitotic rate**
Gastric GIST$^{\Delta}$				
IA	T1 or T2	N0	M0	Low
IB	T3	N0	M0	Low
II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
IIIA	T3	N0	M0	High
IIIB	T4	N0	M0	High
IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate
Small intestinal GIST$^{\lozenge}$				
I	T1 or T2	N0	M0	Low
II	T3	N0	M0	Low
IIIA	T1	N0	M0	High
	T4	N0	M0	Low
IIIB	T2	N0	M0	High
	T4	N0	M0	High
IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification.

* If regional node status is unknown, use N0 not NX.

¶ Histologic grading, an ingredient in sarcoma staging, is not well suited to GISTs, because a majority of these tumors have low or relatively low mitotic rates below the thresholds used for grading of soft tissue tumors, and because GISTs often manifest aggressive features with mitotic rates below the thresholds used for soft tissue tumor grading (the lowest tier of mitotic rates for soft tissue sarcomas being 10 mitoses per 10 HPFs). In GIST staging, the grade is replaced by mitotic activity.

Δ Also to be used for omentum.

◊ Also to be used for esophagus, colorectal, mesentery, and peritoneum.

AJCC cancer staging handbook from the AJCC cancer staging manual 16.[75]

This biggest group of GIST has been further classified into different subtypes based on morphologic differences, and these types are- sclerosing spindle cell, palisading vacuolated subtype, and sarcomatous spindle cell.[66] Collagen deposition is a characteristic finding, which makes these tumors PAS (periodic acid-Schiff stain) positive. Epithelioid GISTs comprise of round to polygonal cells and this type accounts for 20% of the remainder tumors; different characteristic morphologic patterns allow histopathologists to subtype epithelioid variant into sclerosing and hypocellular to sarcomatous and mitotically active to highly active subtypes.[63,65,67]

Immunohistochemical examination not only narrows the differential diagnoses but also provides a choice of chemotherapeutic regimen. More than 95% of the GISTs express CD117/KIT, but it is no longer considered an absolute requirement. KIT expression in GIST is a constitutional feature and not a consequence of mutation.[15,16,40] Other, commonly expressed but less GIST-specific antigens are CD34 and nestin. GISTs are variably positive for smooth muscle markers (smooth muscle actin [SMA], heavy caldesmon, calponin, and embryonic smooth muscle myosin) but are generally negative for desmin. Positivity for S100 protein is rare, and glial fibrillary acidic protein is absent. Keratin 18, and to a lesser degree, keratin 8, are occasionally expressed.[15]

Although KIT is expressed by the majority of GISTs but some other tumors are consistently KIT-positive. It includes a wide range of different tumors like, mastocytoma, seminoma, pulmonary small cell carcinoma, and extramedullary myeloid tumor (granulocytic sarcoma). However, these KIT expressing tumors are so different by their clinicopathologic features to pose any diagnostic dilemma. Other abdominal or GI tumors that are variably KIT positive include metastatic melanoma and the related clear cell sarcoma (30%–50%), Ewing sarcoma family of tumors (50%), childhood neuroblastoma (30%), angiosarcoma (50%), and some carcinomas.[15]

Less than 5% of GISTs do not express KIT, these tumors possess either mutant PDGFRA or KIT wild type. PDGFRA positive GISTs have a predilection for stomach, omentum or peritoneum, and usually reveal epithelioid or mixed type.[38,68]

Protein kinase C theta (PKC theta) is a downstream effector in the KIT signaling pathway activated following KIT activation and suggested as a therapeutic kinase target.[69] Various studies have shown that PKC theta is overexpressed in GISTs, but not in other sarcomas. These studies established PKC theta as a diagnostic marker for GIST.[70-72]

DOG1, a new gene so named being ‘‘discovered on GIST’’ and encoding for a protein of unknown function, seems to be expressed in GIST independent of mutation type and is absent in non-GISTs. Since 5 to 7% of PDGFRA GISTs mutation and 5% of kit-mutated GISTs do not react to CD117/KIT, DOG-1 staining would be an essential tool for a more reliable diagnosis on GISTs.[73,74]

Prognosis, Grading and Staging

The recurrence and risk of relapse of GISTs can be assessed by tumor size, mitotic rate, primary site, surgical margins, and tumor rupture. Out of these, two factors are considered to be the most important, tumor size and mitotic rate by 2002 Consensus risk classification.[63]

In more recent, the TNM staging (AJCC, 7th edition, 2010), grading is based on mitotic rate (Table 1).[75] Based on mitotic rate, GISTs are classified into low (mitotic rate less than 5/50 HPFs) and high grade (more than 5/50 HPFs). However, the staging criteria are different for gastric GISTs and small intestinal GISTs to emphasize a more aggressive clinical course of small intestinal GISTs even with similar tumor parameters.[76] The International Union against cancer (UICC) devised a classification and staging system for GIST.[77] This classification is more coherent with standardized surgical and oncological treatment and follow-up of the patients with GIST (Table 2).[78]

Treatment

Surgery

Complete surgical resection of the GIST is the only potential curative treatment, if the tumor is amenable to it.[79,82] Lymphnode metastasis is rare, so regional lymphnode dissection is generally not required.[80,83] However, about 40- 90% of the surgically treated patients show tumor recurrence later.[84] Furthermore, tumors with bad prognostic signs (mitotically active large tumors of the small intestine) are more likely to recur especially the tumors, which rupture intraperitoneal and bleed.[81,85,86]

Adjuvant Therapy

Surgery alone has proved inadequate in many of the high-risk tumors and GISTs are known for their unresponsiveness to conventional chemotherapy and radiotherapy. With the success of imatinib in the treatment of metastatic GIST, this has prompted investigation into the potential benefit of adjuvant

Table 2 UICC TNM classification for GIST, 7th Edition, 2010

Mitotic rate (50/HPFs)	Tumor size	T		N	M	UICC stage	
		Gastric	Non-gastric			Gastric GIST	Non-gastric GIST
5	2	T1	T1	N0	M0	IA	I
	2-5	T2	T2	N0	M0	IA	I
	5-10	T3	T3	N0	M0	IB	II
	>10	T4	T4	N0	M0	II	IIIA
>5	2	T1	T1	N0	M0	II	IIIA
	2-5	T2	T2	N0	M0	II	IIIB
	5-10	T3	T3	N0	M0	IIIA	IIIB
	>10	T4	T4	N0	M0	IIIB	IIIB
Any	Any	Any	Any	N1	M0	IV	IV
		Any	Any	Any	M1	IV	IV

Abbreviation: UICC, the international union against cancer; GIST, gastrointestinal stromal tumor; HPF, high-power field
TNM classification of malignant tumors.[77]

imatinib. Imatinib mesylate inhibits activation of the KIT and PDGFα proteins by binding to the adenosine triphosphate binding pocket required for receptor phosphorylation and activation.[87] Based on the efficacy of Imatinib, in 2008, it was approved by the U.S. Food and Drug Administration (FDA) as adjuvant therapy for high-risk patients following complete surgical resection of GIST.

Although, excellent results are seen with imatinib therapy but some side effects like fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash can be seen. Some of the adverse-effects are tolerated with time. The more serious side effects include liver dysfunction, lung toxicity, low blood counts and GI bleeding can be worrisome.[88-92] Congestive heart failure has been noted in 8.2% of patients, manageable with medical therapy. Arrhythmias and acute coronary syndromes can complicate the course in some patients.[93]

Sunitinib, an inhibitor of KIT, PDGFRs, VEGFT 1, 23, FLT3, and RET, was approved as a second-line therapy for advance GISTs after imatinib resistance and/or tolerance.[16,35,94] Sunitinib potentially inhibits double mutation of the ATP binding pocket which is not amenable to imatinib, but has little activity against double mutation in the activation loop, making it more potent against imatinib-resistant ATP binding pocket mutation but inferior potency against the activation loop.[35] However, as with imatinib, sunitinib is also not free from side effects. Sunitinib can cause serious, life-threatening adverse effects, including hypertension, cardiotoxicity, and hypothyroidism.[95-97]

Neoadjuvant Therapy and Preoperative Tumor Downstaging Therapy

Promising results have been shown by preoperative systemic therapy for GIST. Preoperative therapy can be used as either neoadjuvant therapy or preoperative tumor downstaging therapy. Neoadjuvant therapy makes surgical outcome better and favorable in a cases of resectable GISTs while, tumor downstaging is a new concept in the management of unresectable malignancy. This option allows surgeons to resect locally advanced unresectable tumors or the tumors complicated by distant metastasis.

As a preoperative downstaging therapy, imatinib has shown promising results and favorable outcomes clinically in patients with unresectable GISTs. Imatinib is indicated when primary resection would carry a higher risk of severe postoperative functional deficit.[87] It is also indicated in those who have a widespread metastatic disease or a recurrence after resection.[87,98-105]

Treatment for Unresectable, Metastatic or Recurrent Disease

The advent of imatinib has revolutionized management of GIST especially in the advanced or unresectable tumors. As many as 50% of the newly diagnosed cases present with locally advanced or metastatic disease. Currently, imatinib is the first-line treatment for metastatic or unresectable GIST. In these cases, it is typically initiated at a dosage of 400 mg per day. This blockade results in a dramatic tumor response in 50%-70% of patients with advanced GIST, associating with a median progression-free survival and a median overall survival of 18-20 months and 51-57 months.[106-108]

Tumor progression on first-line therapy with imatinib is caused by either initial resistance or more often a secondary mutation in tyrosine kinases *KIT* or *PDGFR*. The standard approach in these cases 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.[109] 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-weeksoff regimen.[95]

Assessment of Therapy

Imaging techniques, using contrast enhanced CT scan is the modality of choice to assess course of disease, as recommended by National Comprehensive Cancer Network (NCCN).[110,111] However, MRI should be used for rectal GISTs, additionally PET or PET-CT can also be utilized to assess the tumor progression or regression.[112]

Treating a Resistant Tumor

Emerging resistant to imatinib and sunitinib provoke the search of newer TKIs. Nilotinib, a newer TKI has demonstrated activity against imatinib and sunitinib resistant GISTs.[113] An ongoing pilot study has displayed substantial clinical benefit of nilotinib and has found it safe in the first-line treatment of advanced GIST. [114] Other agents, such as dasatinib,[115] sorafenib,[116] and masitinib[117] target multiple oncogenic receptor tyrosine kinases that have been implicated in the development and growth of GIST.

Regorafenib, a recent addition to second generation TKIs is a multikinase inhibitor with activity against KIT, PDGFR and VEGFR and is well tolerated, with common adverse effects being hypertension (23%), hand-foot skin reaction (20%) and diarrhea (5%).[88,118,119] These newer agents and a wide number of others[120] are currently under clinical trials for the management of advanced and resistant GISTs and likely to change the treatment of this disease soon.

CONCLUSION

Once, an enigmatic tumor of ambiguous origin has now been deciphered to its molecular level with some lacunae left. We have learnt a lot about GIST from investigators around the world that how a solid tumor with simple genetics can cause diagnostic dilemma. Now it is not as gloomy as it was in the past, modern molecular therapy provided us the knack to deal with this tumor. Large multi-institutional studies are providing valuable information to us. We hope that upcoming researches will improve our understanding and improve the outcome in these patients.

“Life throws challenges and every challenge comes with rainbows and lights to conquer it.”

-Amit Ray

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