CANCER NEWS

Focus Area:
GASTROINTESTINAL STROMAL TUMORS

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From the Desk of Director Research

Gastrointestinal stromal tumors (GIST) are a subset of mesenchymal tumors and represent the most common mesenchymal neoplasms of the gastrointestinal (GI) tract. They have emerged from being poorly defined, treatment resistant tumors to a well recognized, well understood and treatable tumor entities within a decade. They account for less than one percent of all GI tumors. Their origin was first attributed to Cajal's cells in mesodermal tissue but it has now been recognized that GIST arise from multipotential mesenchymal stem cells.

In the past, these tumors were presumed to have elements of smooth muscle, so they were defined as leiomyomas, leiomyosarcomas and leiomyoblastomas. The term GIST was first coined by Mazur and Clark in 1983 in order to describe a heterogenous group of gastrointestinal non-epithelial neoplasms. Approximately 85% of GIST harbor activating mutations in KIT or the homologous receptor tyrosine kinase platelet-derived growth factor receptor alpha (PDGFRA) gene. GIST are characterized by gain-of-function mutations in the KIT proto-oncogene, most commonly involving exon 11, less frequently exon 9, and rarely exon 13 or 17. In GISTs without KIT mutations, gain-of-function mutations may occur in the PDGFRA gene, thereby providing an alternative oncogenic mechanism. These mutations are an early event in GIST development and the oncoproteins serve as a target for small molecule tyrosine kinase inhibitors such as imatinib, and sunitinib.

The incidence of GIST is estimated to be approximately 10-20 per million, per year. The annual incidence in Europe is approximately 8,000-9,000 cases and in the USA of about 4,000-5,000 cases a year. However, the precise incidence is unknown because of the incomplete definition and classification. Malignancy possibility is 20-30%. The most common location of GIST is stomach (50-60%) and small intestine (30-40%). Five to ten percent of the GIST arise from the colon and rectum and 5% are located in the esophagus. At the time of diagnosis, the majority of patients are between 40 and 80 years old, with a median age of approximately 60 years. GISTs have no clear gender predilection. Rarely, GIST occur in children and young adults.

The clinical presentation of GIST is variable but the most usual symptoms include the presence of a mass or bleeding. Surgical resection of the local disease is the mainstay therapy. However, therapeutic agents, such as imatinib have now been approved for the treatment of advanced GIST and others, such as everolimus, rapamycin, heat shock protein 90 and insulin-like growth factor, are in trial stage and demonstrate promising results for the management of GIST.

The present issue of the Cancer News highlights the newer advances in the field of "Gastrointestinal Stromal Tumors" and features the regular articles, such as Special Feature, Guest Article, Perspective and In Focus. We are grateful to Dr Nishitha Shetty, Assistant Professor, Dept of Medical Oncology, Father Mullers Medical College Hospital, Mangalore; Dr Shailesh V Shrikhande, Professor of Surgical Oncology, Dept of GI and HPB Surgery, Tata Memorial Centre, Mumbai; Dr Bhawna Sirohi, Head of Medical Oncology, Dept of Medical Oncology, Mazumdar Shaw Cancer Centre, Narayana Health, Bangalore for the "Guest Article".

Suggestions/ comments from the readers are welcome.

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SPECIAL FEATURE

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SURGICAL MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS

Introduction

GIST represent the most common mesenchymal neoplasms of the Gastrointestinal tract. With an annual incidence of 11-14 per 106, they form 0.1%-3.0% of gastrointestinal malignant tumors .In the past, there had been considerable debate regarding its nomenclature, cellular origin, diagnosis and prognosis. Due to their similar appearance by light microscopy, GISTs were previously thought to be smooth muscle neoplasms and grouped with leiomyomas, leiomyoblastomas, leiomyosarcomas or schwannomas. It was in 1998, after the discovery of gain-of-function mutations in the c-KIT protooncogene that these tumors were reliably distinguished from other histopathological subtypes of mesenchymal tumors.

GISTs (> 95%) are positive for CD117. In 60%-70% of the patients, IHC for CD34 (mesenchymal / hematopoietic precursor cell marker) is also positive. Vimentin and smooth muscle actin is positive in 15% to 60%. GISTs. (10%-15%) have no detectable KIT or PDGFRA mutations [wild-type GIST (WT-GIST)]. Absence of mutations does not exclude the diagnosis of GIST. DOG1 is a calcium dependent, receptor activated chloride channel protein expressed in GIST; this expression is independent of mutation type and can be used in the diagnosis of KIT-negative tumors.

Clinical Presentation

Only 70% of the patients with GIST are symptomatic, where as 30% are asymptomatic and the tumors are detected incidentally. Symptoms and signs are not disease specific; they are related more to the site of the tumor. In stomach, bleeding comprises the most common symptom followed by vague abdominal discomfort. They cause dysphagia in the esophagus, biliary obstruction around the ampulla of Vater or even intussusception of the small bowel. Lymph node metastases are uncommon in GIST. Distant metastases most commonly occur in the peritoneum, omentum, mesentery and the liver. They have a high tendency to seed and hence intraperitoneal or even scar metastases are known to occur.

Due to the vague and protean presentation of GIST, initial diagnosis can be delayed. Diagnostic imaging depends upon the site. For lesions of esophagus and stomach upper gastrointestinal endoscopy with or without biopsy is the investigation of choice. For staging of the GISTs contrast enhanced computed tomography (CECT) is the modality of choice (Fig 1). It is used to characterize the lesion, evaluate its extent, and assess the presence or absence of metastasis.

GISTs are positron emission tomography (PET) avid tumors because the receptor tyrosine kinase increases the glucose transport protein signaling. PET is useful in revealing small metastases which would otherwise not have been picked up on CECT and now is being routinely used in the staging of GISTs.

Preoperative Biopsy

Due to the high risk of rupture, bleeding and tumor dissemination, pre-operative biopsy should be avoided in all potentially resectable tumors in
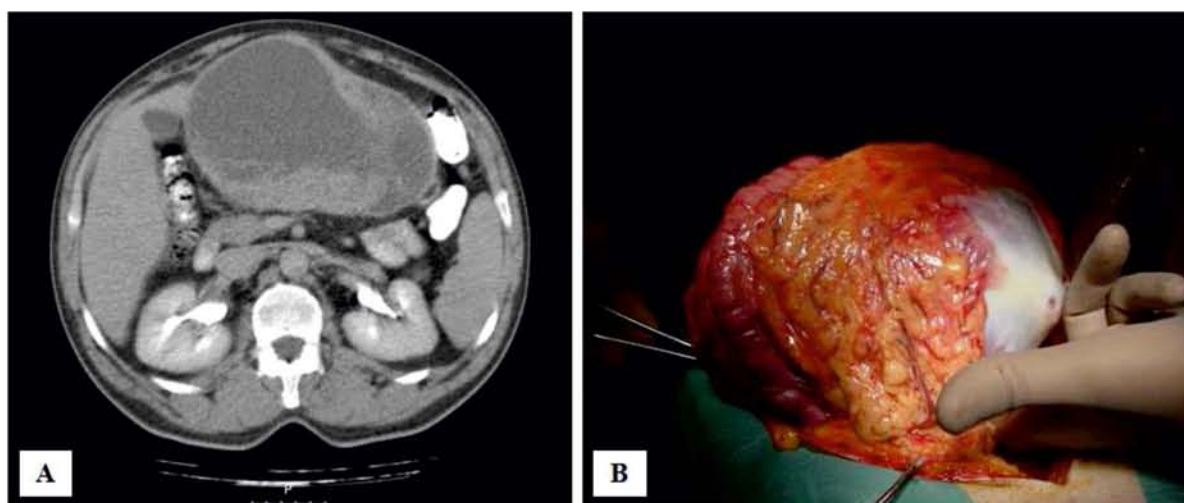
Fig. 1. (A) CT scan of a large dimension GIST invading adjacent transverse colon; (B) Macroscopic aspect of the surgical specimen with R0 resection

patients at low surgical risk. Conventional endoscopic sampling techniques, such as forceps biopsy, are limited in their clinical utility given the difficulty of sampling lesions in a submucosal location and the increased risk for perforation. The accuracy of EUS guided needle aspiration (EUS-FNA) is 80%-85%. A clear role for EUS guided trucut biopsy is yet to be defined, given the inconsistent results in providing adequate tissue yield.

Biopsy would only be indicated in cases of metastatic disease or unresectablility where neoadjuvant treatment is being considered and in cases where there are serious diagnostic doubts with other tumoral lesions treated differently than GIST, such as ectopic pancreas, lymphomas, oesophageal leiomyomas, etc., and especially in patients with high surgical risk. Intraoperative frozen biopsy would only be indicated if the possibility of lymphoma or adenocarcinoma is excluded during the course of surgery for a potential GIST.

Risk Stratification

Prognosis in GIST is highly variable. The critical determinants of GIST behavior include tumor size, mitotic rate, and location. Small tumors (<2 cm) with low mitotic rates (<5 per 50 high power fields [HPF]) show benign behavior, whereas larger tumors (>5 cm) with high mitotic rates (>10 per 50 HPF) are associated with malignant behavior and display higher rates of recurrence after surgical resection. Tumors located in the stomach have favorable outcomes relative to small bowel tumors. Of the 3 determinants of behavior mentioned earlier, mitotic rate is considered the most significant. R0 resection is considered to be most important risk factor determining the outcome. Tumor rupture before or during dissection portends a

worse outcome manifested by higher rates of peritoneal recurrence.

Gene locus as well as the type of mutation can also affect prognosis. Molecular analysis of the KIT proto-oncogene has revealed that tumors with exon 9 mutations or deletions in exon 11 are more aggressive compared with those harboring either a point mutation or insertion in exon 11. Recurrence after surgery is more common in patients with a deletion mutation in exon 11. In patients with PDGFRa mutations, location of the tumor is also important. Mutational analysis is also important to determine the response to immunotherapy. Exon 18 D842V mutations are resistant to imatinib therapy, whereas those in exon 12 are responsive to imatinib. Wild type GISTs are associated with imatinib resistance and portend an unfavorable prognosis.

Surgical Management of GIST

Objectives and Surgical Techniques: GIST tumors have a number of features that determine the surgical treatment. These tumors can develop liver and peritoneal metastases but rarely lymphatic ones, making lymphadenectomy unnecessary. They show exophytic extraluminal growth, which makes them easy to find. They have an expansive, not infiltrative growth, limiting the resection to be performed. They are very fragile, highly vascularised tumors. Thus care must be taken in their handling during surgery in order to prevent spillage. The main objective of primary localised GIST surgery is complete enbloc resection. In most cases these resections can be carried out through very limited resections of segments or 'wedges' of the tumor. In other cases more extensive anatomical resections, including resection of adjacent organs as a unit or "block" is required. The resection of a GIST must not be disruptive, that is, it must preserve the

Table 1: Prognostic factors for recurrence after primary surgery for GIST

Site	Very low risk	Low risk	Moderate risk	High risk
Gastric GIST	2-5 cm = 5/50 HPF	5-10 cm =5/50 HPF:	>10 cm +5/50 HPF: 2-5 cm >5/50 HPF	5-10 cm, >5/50 HPF or >10 cm, >5/50 HPF
Small bowel		2-5 cm, +5/50 HPF	5-10 cm, +5/50 HPF	>10cm, =5/50 HPF 2-5cm, >5/50 HPF 5-10cm, >5/50 HPF >10cm, >5/50 HPF
Duodenal		2-5cm, 5/50 HPF		>10cm, =5/50 HPF 2-5cm, >5/50 HPF 5-10cm, >5/50 HPF >10cm, >5/50 HPF
Rectal		2-5cm, =5/50 HPF		>10 cm, =5/50 HPF; 2-5 cm, >5/50 HPF; >10 cm, >5/50 HPF, 5-10 cm > or <5/50 HPF

Table 2: Depending on tumor size and mitotic rate

Risk	Tumor size and mitotic index
Very low risk	<2 cm, <5/50 HPF
Low risk	2-5 cm, <5/50 HPF
Intermediate risk	<5cm, 6-10/50 HPF; 5-10 cm, <5/50 HPF
High risk	>5cm, >5/50 HPF; >10 cm, any mitotic rate; any size >10/50 HPF

pseudo-capsule and not break the tumor. In fact, spillage results in R2 resection.

Management of Primary Localized Disease

Small GIST: There is a general consensus that the definitive treatment of primary GISTs with dimensions 2 cm and without evidence of peritoneal dissemination or distant metastases is complete macroscopic surgical resection1.

Tumors which are less than 2 cm in the widest dimension are defined as small GIST. They are usually discovered incidentally on endoscopy. If these lesions are symptomatic, complete surgical resection is recommended. Small asymptomatic gastric GISTs (less than 2 cm) with no high-risk EUS characteristics (large dimension, irregular extraluminal limits, heterogeneous echo pattern, presence of cystic areas, and hyperechoic foci) features can be managed conservatively with endoscopic surveillance at 6 to 12 months intervals. Endoscopic resection (ER) of these small tumors would be another option.

Role of Laparoscopy

Open surgical resection was the standard of treatment until two decades ago. Lukaszczry and Pretez in 1992 were the first to report a successful laparoscopic resection of a gastric GIST. Laparoscopic resection is most commonly done in gastric GIST followed by small bowel. Until now, there have not been any randomized controlled trials comparing the open vs laparoscopic approach, and all recommendations have been based on observational studies.

Although NCCN guidelines suggest that laparoscopic resection is indicated in tumors less than 2 cm, many surgeons have reported a safe excision of tumors > 5 cm and others up to 10 cm.

The laparoscopic techniques can be divided into different subtypes: transgastric resections, endoscopy assisted laparoscopic resections, wedge resections, partial gastrectomy and hand-assisted laparoscopic resections. The surgical approach depends on tumor size and location.

Anatomical Tumor Location and Surgical Techniques

Oesophagus: Oesophageal GISTs represent only 1% of the GISTs. They are easily confused with leiomyomas. Esophagus lacks a serosal covering, so the risk of tumor rupture is extremely high. A complete resection of tumor that does not have evidence of metastasis should be the initial therapy if the tumor is technically resectable with acceptable risk of morbidity. Oesophageal GISTs' resections are essentially limited to either simple enucleation or oesophagectomy. However, which surgical procedure should be performed remains controversial. Preoperative identification of tumor site is more important than tumor size for deciding optimal surgical strategy.

In the distal oesophagus, oesophagectomy is better alternative to enucleation for large tumors and those close to the gastroesophageal junction. Small tumors (<5 cm), confined to the oesophageal wall in patients at high risk, could be locally resected (enucleated) as long as negative resection margins are obtained.

Stomach

The type of surgery depends upon the location and the size of the tumor. In a series of 140 patients, 68% were treated by 'wedge' resection, 28% with partial gastrectomy and only 4% required a total gastrectomy. Most surgical series did not find differences in terms of long-term survival between gastrectomy and 'wedge' resection. Occasionally, large gastric tumors are firmly adhered to neighbouring structures, requiring aggressive and extensive 'block' resections. Laparoscopic surgery is most commonly done in patients with gastric GIST.

If the tumor is located on the anterior wall or greater curvature, wedge resection can be done and for the posterior wall tumor if the lesion is endophytic, gastrotomy and wedge resection is done and for exophytic lesion wedge resection after dividing gastrocolic ligament is done.

For lesion in distal 1/3- distal gastrectomy and proximal 1/3 near gastroesophageal junction – intragastric / transgastric approach is preferred. For larger tumors, hand-assisted technique is preferred because it allows for better exploration and easier handling and dissection of the tumor.

Duodenum

They account for 4.5% of all GISTs and are usually located in the 2nd duodenal portion. Three basic surgical techniques have been described: local 'wedge' excision with primary duodenal closure, segmental duodenal resection plus duodenojejunostomy and Whipple's pancreaticoduodenectomy (WPD).

The choice of any of these techniques depends on the tumor size and the distance from the ampulla of Vater as well as its relationship with pancreatic duodenal face. Local 'wedge' resection, although technically possible in small duodenal tumors, appears to be worse than segmental resection due to a greater number of local recurrences. However, survival and recurrence between WPD and segmental resection are similar. These data favor the use of segmental resection since it is better than local excision without the morbidity/mortality of WPD.

General and in case of very small tumors (<1 cm) and more than 2 cm from the ampulla, it is possible to use a 'wedge' excision, while large tumors (>3 cm) located in the 3rd-4th duodenal portion are treated with segmental resections. WPD is reserved for periampullary tumors or those >3 cm located in the 1st and 2nd part of the duodenum, where segmental resection is technically impossible.

Small Intestine

The small intestine is the second location by order of frequency and the technique of choice is segmental resection either laparoscopic or open. In special locations such as the Treitz angle, it is preferable to perform resection followed by duodenojejunostomy.

For large tumors (>5 cm) or those close to the Treitz, an open approach is preferable. Many of these tumors often invade adjacent organs, which requires extensive resections. Given its exophytic growth along with its impact on the serosa, there is a high possibility of for peritoneal tumor dissemination. This explains the high rates of peritoneal metastasis.

Colon

Colon is a very infrequent location (<5% of the total) and the technique of choice is segmental colectomy without lymphadenectomy. These tumors commonly have high risk features (70% of these GISTs). A recent publication by the Memorial Sloan Kettering Cancer Center2 calculated that the disease-free survival rate for these tumors was only 20% at six years. Segmental resections are the preferred technique depending upon the location of the tumor.

Rectum

Rectum is the third location in order of frequency. A high rate of incomplete resections (R1) is associated with this location, reaching up to 38% of cases. The technique of choice depends on tumor size and location. For small tumors (<3 cm) with low extra-rectal growth trans-anal excision can be performed. For large tumors (>5 cm) that have a large anterior or posterior extra-luminal component, a trans-sacral (Kraske) or trans-vaginal approach is recommended. For larger tumors and those distally located, the technique of choice is abdomino-perineal resection.

The potential role of neoadjuvant imatinib therapy prior to surgery has been examined in an attempt to make a tumor technically resectable and to perform a less aggressive surgery with lower morbidity / mortality, with the particular aim of preserving the sphincter. The available literature consists mainly of individual cases and very few case series. The series of Haller4 presents their experience with 10 rectal GISTs, of which six were locally advanced and four were low rectal. In all cases an R0 resection was achieved without requiring the use of colostomy. Neoadjuvant therapy improves tumor resectability and the possibility of organ preservation due to reduction in size.

Importance of Disease Free Margin

The 2004 NCCN guideline states that positive microscopic margins or R1 doesn't compromise the survival. However, the 2007 update includes negative microscopic margins as a goal. The available series report conflicting results. De Matteo5compared 65 cases of R0 with15 cases of R1. This author, like others, found no differences in either the recurrence rate (33% versus 30%, respectively) or in survival, thereby emphasizing complete macroscopic resection. In sharp contrast, De Gouveia6 compared 78 cases of R0 versus 18 cases of R1. The recurrence rate for R0 was 9% versus 27% for R1. There are only a few small series that address this problem and they suffer from selection bias by including, in different proportions, tumors with various risk factors, such as size or

tumor grade. There is an association between size, tumor grade and incomplete resection, that is, it is easier to achieve an R0 resection in small, low-grade tumors and vice versa. Since low-grade tumors generally require less aggressive surgeries, this explains why some studies report that local resections have lower recurrence rates than segmental resections.

Full macroscopic resection with a 1cm margin is more than sufficient. Indeed, a safety margin of 1-2 cm, which includes the 5 mm of potential microscopic tumor extension, achieves an R0 resection in all cases. For locally advanced tumors, the recommendation is to attempt macroscopic tumor resection without paying attention to the potential microscopic involvement of the margins, if this avoids resection of vital structures. Except in cases of palliative surgery, R2 resection is not an option. Another problem that arises is about what to do if the final pathology report reveals an R1 resection. To date, there is no evidence that the presence of positive margins after macroscopic resection of a GIST requires re-resection.

Neoadjuvant Therapy

Surgery is the primary treatment for all tumors which can be resected without significant morbidity. If this is not the case, then preoperative imatinib should be considered. Imatinib is effective in reducing the size of the tumor prior to resection, increasing the likelihood of negative margins without significant morbidity. Before starting a patient on neoadjuvant imatinib, a baseline CECT is recommended. The optimal duration of preoperative therapy is yet unknown. In patients responding to therapy, imatinib is continued until maximal response (defined as no further

improvement between 2 successive CT scans). This can be as long as 6-12 months but it is not always necessary to wait for a maximal response prior to surgery. Surgery is recommended when the tumor appears to have downsized to a point where complete resection can be achieved without significant morbidity. Imatinib should be stopped just before surgery and resumed as soon as the patient is able to tolerate oral medications, regardless of the surgical margins. The recommended dose is 400 mg/d, with dose escalation to 800 mg /d in cases of documented mutations in KIT exon 9. In cases where there is no progression, continuation of the same dose of imatinib is recommended and resection is considered. If there is tumor progression, as confirmed with CECT scan, surgery is recommended after discontinuing imatinib.

Unresectable, Metastatic or Recurrent Disease

Imatinib has a very high likelihood of clinical benefit and a positive response in patients with documented unresectable GIST. Imatinib is indicated when primary resection would carry the risk of severe postoperative functional deficit. It is also indicated in those who have a widespread metastatic disease or a recurrence after resection. There is a survival benefit of cytoreductive surgeryfollowing preoperative imatinib in patients responding to it. The lesion is assessed within 3 months of initiating therapy to determine if it has become resectable. In cases where the tumor remains unresectable,imatinib is continued indefinitely until there is evidence of tumor progression. Continuation of TKI therapy life-long for palliation of symptoms forms an essential component of best supportive care. Options for
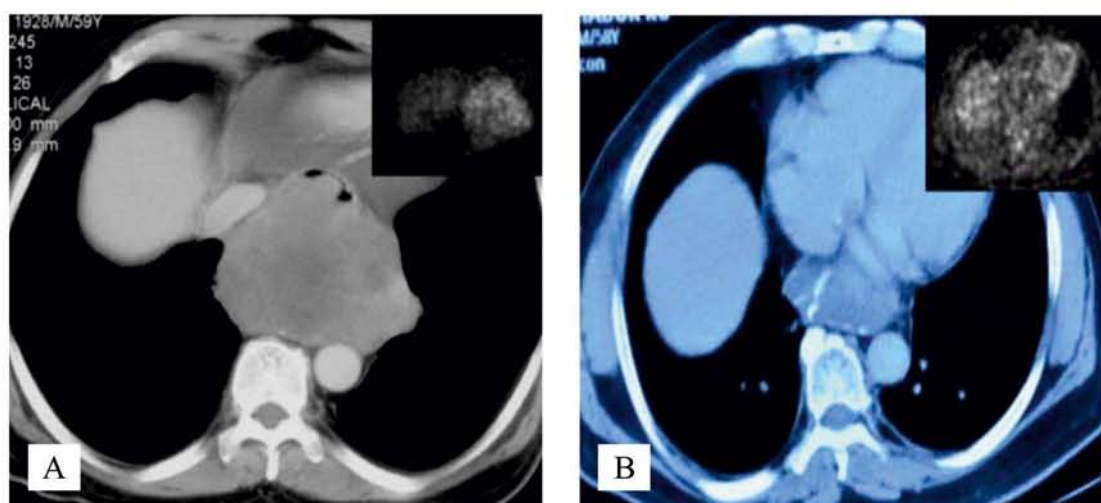

Fig. 2. (A) CT scan showing locally advanced GIST of esophagus with PET CT in inset
(B) CT Scan showing locally advanced GIST of esophagus with PET CT in inset after Neoadjuvant imatinib

patients with progressive disease or with widespread systemic disease and good performance status (0-2) include continuation of imatinib at the same dose, dose escalation up to 800 mg in the absence of severe adverse drug reactions or switching to sunitinib.

Peritoneal and Liver Metastases

Patients, who are medically fit with surgically accessible localized disease, should be considered for resection. Debulking in the form of removal of the gross tumor followed by intraperitoneal chemotherapy with cisplatin and doxorubicin or mitoxantrone has been attempted; the median time to recurrence was increased from 8 to 21 months with the addition of intraperitoneal chemotherapy7. Surgery in metastatic patients is a case based decision. Residual tumor resection is safe but multifocal resection is not recommended without considering the patient's performance status and personal situation. When surgery may not be possible, limited evidence exists that similar benefits could be obtained with nonsurgical ablative techniques, such as radiofrequency ablation or embolization. In carefully selected patients with GIST liver metastases, radiofrequency ablation has been shown to be a safe and useful therapeutic option. Liver transplantation for patients with metastatic GIST has been attempted with guarded results. Serralta8 et al performed a transplant in three patients for tumors which on histopathology turned out to be GIST; all their patients had a recurrence after a median period of 3 years and survival was extended by starting them on imatinib.

Surveillance

GISTs have unpredictable behavior and long term follow up is essential for all patients, independent of their benign or malignant characteristics. As the majority of GISTs tend to recur within the first 3-5 years, intense follow up is required during this period. Follow up is recommended both for persistent gross residual disease and for completely resected disease. Clinical examination with CECT abdomen every 3-6 months is the recommended surveillance protocol. Use of PET scan as a follow up modality is also picking up pace.

Conclusion

GISTs are the most common mesenchymal tumors of the GI system. Improved knowledge of the oncogenic drivers and resistance mechanism operant in GIST has acted as a foundation for the general understanding of the role of targeted therapies in human cancers. Surgery is the primary treatment of choice in localized or potentially resectable GIST. Surgery and imatinib form the first-line therapy and their effectiveness for the majority of patients has been revolutionary. Sunitinib is an approved second-line agent which is effective in many non-responders to imatinib therapy. Personalizing the treatment of GISTs and tailoring treatments to tumor genotype using combination therapies in order to prevent emergence of resistance is essential to optimize patient.

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GUEST ARTICLE

TARGETED THERAPY FOR GASTROINTESTINAL STROMAL TUMORS

Introduction

Gastrointestinal stromal tumors (GIST) are the most common gastric mesenchymal tumors. In recent years, it has gained popularity due to the identification of c-kit mutation and a specific target to it which is imatinib, which has made a landmark milestone in the evolution of GIST therapy. The median age of presentation is 5th to 6th decade and the commonest location is stomach. Although surgery remains the time tested treatment for localized GIST, targeted agents like imatinib have widened the treatment options in both early and advanced GIST. In this article, we present a brief review of pathophysiology followed by details on various targeted agents which are currently available.

Pathology

Tissue biopsy shows fascicles of spindle cells with eosinophilic cytoplasm, nuclear palisading, inconspicuous nucleoli and extracellular collagen1. Due to the mixture of lymphocytes and apoptotic debris, the tumors appear to be having a high mitotic index. The calculation of mitotic index is necessary to predict the recurrence risk. The current recommendation is to calculate the mitotic count in 50 high power fields (HPF), with each field being 10mm. Based on pathology, there can be 3 types of morphological GISTs: spindle (70%), epitheloid or mixture of both[1]. On immunohistochemistry (IHC), the hallmark is CD117 positivity which is seen in approximately 95% of tumors. Other positive markers markers are BCL-2 and CD34. Around 95% of tumors are desmin negative with variable expression of smooth muscle actins and S100 protein (10%). DOG-1 (discovered on GIST) is a recently discovered marker, positive in GIST, irrespective of the type of mutation[2].

Molecular Pathophysiology: CD117 (KIT) mutation encoded by the KIT proto-oncogene present on chromosome 4 is the most common mutation seen in GIST[3,4]. CD 117 is normally expressed in the gastro intestinal interstitial cells of Cajal[5]. It is positive in 80 to 85% of the tumors. The ligand for KIT receptor is called the stem cell factor (SCF) (Steel factor). During normalcy, SCF binds with its receptor causing homodimerisation leading to a cascade of events which causes cell proliferation. However during malignancy, due to driver mutations the same cascade gets self activated and leads to excessive cell proliferation[6]. The pathways which get activated are the Ras/Raf/MAPK , JAK-STAT, IGF, PI3K/AKT and mTOR pathways[7,8]. Exon 11 KIT mutations are the most common (65-70%), that happen in the juxtamembrane domain, seen more in stomach tumors and show good imatinib response. In contrast, exon 9 mutations are less common (5-10%), and happen in the extracellular domain, seen more in intestinal tumors and show poor imatinib response. Other mutations could occur in the ATP binding domain of exon 13 and 14 or at the activation loop of the kinase domain of exon 175. In patients whose tumors are KIT negative, 30-40% will be positive for platelet derived growth factor receptor alfa (PDGFRA) and the usual location is stomach. Most commonly, PDGFRA mutations occur in activation loop domain of exon 18 and less commonly in juxtamembrane domain of exon 12 or ATP binding domain of exon 14[9]. Wild type GISTs which are negative for both cKIT and PDGFRA mutations are usually seen in the paediatric population. KIT negative tumors are better than KIT positive tumors, especially KIT (mutations with deletions affecting codons 557–558 being worse. Other GISTs could be familial (mutation in exon 8,11, 13 or 17) or associated with neurofibromatosis 1, Carney's triad or Carney-Stratakis syndrome[10].

Management of Early GIST

Neoadjuvant Imatinib Therapy and Surgery: The main treatment for resectable GIST is surgery and any tumor more than 2 cm should be resected[11] .

The median survival for resectable tumors post surgery is approximately 66 months which gets reduced to 22 months in unresectable tumors6. Since metastases to nodes is rare, routine lymph node dissection is not recommended11. In borderline resectable locally advanced tumors, neoadjuvant imatinib can be given to make the tumor amenable for surgery with margin negativity[12,13]. The duration of neoadjuvant imatinib is not clearly defined. In a database of 10 EORTC STBSG sarcoma centers, patients with locally advanced GIST post neo-adjuvant imatinib were studied. After a median 40 weeks of imatinib, the rate of R0 resection was 83% and the 5 year disease free survival (DFS) was 65% with median OS of 104 months[14]. In another study done at Tata Memorial Hospital, after a median duration of 8.5 months of neo-adjuvant imatinib, the response rate was 79% with a 3 year OS of 100%[15].

Adjuvant Imatinib Therapy

Prior to adjuvant imatinib therapy, nearly half of the operated patients recurred[16]. Hence, adjuvant imatinib after complete gross resection was recommended in tumors with high recurrence risk [16-18]. The important risk stratification systems to predict the recurrence after complete surgical resection are (Table 1).

1. The National Institutes of Health consensus (NIH) criteria (Fletcher's criteria)
2. The Armed Forces Institute of Pathology criteria (AFIP) (Miettinen's criteria)
3. Joensuu's modified NIH classification (J-NIHC)(the 2 modifications were.
a. Tumor rupture was added
b. Non-gastric tumors in the intermediate risk were converted to high risk
4. The American Joint Committee on Cancer Staging System (AJCCS)
5. The Japanese modified NIH criteria

The first three criteria are the most commonly used. Based on good to poor prognosis the site predilection is as follows: gastric, small intestine, colorectal, extra GI GISTs. Based on size, the 10 year recurrence rate for <1cm (micro GIST), 5-10cm and 10-15cm tumors is 0, 50, and 70%

respectively. Based on mitosis, the 10 year recurrence rate for <5 and >5mitoses/HPF is 25% and 70% respectively[19]. According to the modified NIH criteria, the 10 year RFS for very low, low, intermediate and high risk is 95, 90, 85 and 35% respectively[19].

In the MSKCC study, 127 patients with localized primary GIST who underwent complete gross surgical resection were analyzed in which they found that the RFS was 83%, 75%, and 63% at 1, 2, and 5 years, respectively. The factors predictive of increased recurrence were ≥ 5 mitoses /50 HPF, tumor size 10 cm, and small intestine tumours[20]. Gold et al designed a nomogram to predict RFS based on tumor size, location and mitotic index (<5 or ≥ 5/HPF) after surgery in the absence of adjuvant imatinib. The concordance probability was 0.78 (standard error ±0.02). Moreover this nomogram was better than the NIH staging system and equivalent to the AFIP staging system for recurrence prediction[21]. Yanagimoto et al analyzed 712 post surgery GIST patients and evaluated the above systems. They found that the factors significant on multivariate analysis were size >5 cm, mitotic count >5/50 HPF, non-gastric location, and the presence of rupture and/or macroscopic invasion. They also found out that the J-NIHC and AJCCS were

Table 1: NIH, AFIP and Joensuu risk stratification system

Risk stratification (96, 97, 98)	Tumor size (cm)	Mitotic count (per HPF)	Tumor site	Tumor rupture
NIH - Fletcher				
Very low risk	<2	>5		
Low risk	2-5	<5		
Intermediate risk	<5	6-10		
	5-10	<5		
High risk	>5	>5		
	>10	Any		
	Any	>10		
AFIP				
Group 1	=2	= 5		
Group 2	>2 to = 5	= 5		
Group 3a	>5 to = 10	= 5		
Group 3b	> 10	= 5		
Group 4	= 2	> 5		
Group 5	> 2 to = 5	> 5		
Group 6a	> 5 to = 10	> 5		
Group 6b	> 10	> 5		
Joensuu				
Very low	<2	= 5	Any site	
Low	2.1-5	= 5	Any site	
Intermediate	2.1-5	> 5	Gastric	
	< 5	6 - 10	Any site	
	5.1-10	= 5	Gastric	
High	Any	Any	Any site	Yes
	> 10	Any	Any site	
	Any	> 10	Any site	
	> 5	> 5	Any site	
	= 5	> 5	Non gastric	
	5.1 - 10	= 5	Non gastric	

respectively the most sensitive and accurate tools to predict recurrence[22]. Zhao et al further classified the high risk group into very high risk group which included tumors having mitoses count > 10/50 HPF and serosal invasion. Specifically in tumors with serosal invasion, despite adjuvant imatinib the recurrence rates were high, thus stressing the importance of neoadjuvant imatinib so that serosal invasion is reduced[23].

The ACOSOG Z9000 phase II trial studied 107 high risk recurrence (tumor size >10 cm, tumor rupture, or <5 peritoneal metastases) patients with 1 year of adjuvant imatinib 400mg versus placebo. The 1, 3 and 5-year RFS was 96, 60 and 40% and OS was 99, 97 and 83% respectively. While the median RFS was 4 years, the median OS had not been reached[24]. In the subsequent phase III trial (ACOSOG Z9001) patients with tumor >3cm were randomized to adjuvant imatinib versus placebo for 1 year. The RFS was 98 % in the imatinib arm and 83 % in the placebo arm (hazard ratio (HR), 0.35; 95 % confidence interval (CI), 0.22 to 0.53; p<0.0001), especially better in patients with high (size ≥ 10 cm) and intermediate (≥ 6 to <10 cm) risk. However there was no difference in OS which could be as a result of crossover to imatinib arm on progression[25]. These data led to the accelerated FDA approval to adjuvant imatinib in the year 2008 which was later converted to full approval in 2012. Adjuvant imatinib is useful in KIT exon 11 deletions but not in KIT exon 11 insertions or point mutations, KIT exon 9 mutations, PDGFRA mutation or wild type GIST[25].

Subsequently, phase III Scandinavian Sarcoma Group/ Arbeitsgemein-schaftInternistische Onkologie trial XVIII (SSG XVIII/AIO) compared post surgery high recurrence risk tumors (with at least one of the following: longest tumor diameter >10 cm, mitotic count >10/50 HPF, tumor diameter >5 cm, and mitotic count >5 or tumor rupture) with 1 or 3 years of adjuvant imatinib. The 5 year RFS and OS were 66% versus 48% (HR, 0.46; 95 % CI, 0.32 to 0.65; p<0.0001) and 92% versus 82% (HR, 0.45; 95 % CI, 0.22 to 0.89; p=0.02), respectively in the 3-year and 1-year group[17]. 13.6% of patients in the 3 year arm discontinued imatinib due to adverse events compared to 7.5% in the 1- year arm. The most common adverse effects were peri-orbital edema, diarrhea and muscle cramps. Casali et al studied 900 patients with intermediate- or high-risk resected GIST and randomized them to 2 years of adjuvant imatinib versus no adjuvant therapy. The 3-year and 5 year RFS was 84% versus 66 % (p<0.001) and 69% versus 65% (p<0.001) in the

imatinib versus no adjuvant therapy arms, respectively[26]. At present, it is recommended to give 3 years of adjuvant imatinib for high risk tumors after complete gross resection[27]. In the ongoing phase II PERSIST-5 trial (post resection evaluation of recurrence-free survival for gastrointestinal stromal tumors) the benefit of 5years of adjuvant imatinib is being studied.

Management of Metastatic GIST

Role of Surgery: The role of surgery in metastatic tumors is not routinely recommended. The scenarios where it can be used are12:

1) Stable or shrinking disease post TKI therapy when complete gross resection is feasible

2) Tumours showing TKI response at other sites with only isolated clones showing progression

3) For palliation in case of hemorrhage, perforation, obstruction or abscess.

Studies show significant benefit from surgery even in metastatic GIST patients. In a study done in China, the 2-year PFS was 88.4% in the surgery arm and 57.7% in the imatinib alone arm (P = 0.089) while the median OS was not reached in the surgery arm and was 49 months in patients with imatinib-alone arm (P = 0.024)[28]. In another study, the significance of pathological complete response (pCR) post imatinib in metastatic GIST was analyzed, in which patients with pCR had better PFS and OS than those without pCR [2-year PFS and OS: 82.5% and 100% versus 35.6% and 49.4%, (p=0.014 and p=0.004) respectively[29].

First Line TKI Therapy for Metastatic GIST

In the pre imatinib era, the survival of GIST patients varied from 10-20 months. After the advent of imatinib, the survival of advanced GIST patients has extended up to 5 years30, with response rates of 67% in exon 11 KIT mutation and 40% in exon 9 mutations. Initially phase II trials in metastatic tumors showed response rate of 82% with time to treatment progression (TTP) of 24 months and OS of 57 months[30,31]. The EORTC Soft Tissue and Bone Sarcoma Group phase III randomised trial studied 946 patients. They were randomised to receive 400mg or 800mg imatinib. On progression on 400mg, patients were allowed to crossover to the 800mg arm. The response rate in both groups after a median follow up of 2 years was around 50% and overall survival at 1 and 2 years was 85% and 70% in the 400mg and 800mg groups respectively. In the 800mg arm, many received dose reductions[32]. The North American Sarcoma Intergroup study (S0033) covered 746 patients randomised to 800mg versus

400mg imatinib. There was no difference in the objective response rate, PFS and OS between the two groups[33]. Subsequent meta analysis showed that the median OS was 4 years and both 800mg and 400mg were equivalent; however patients with exon 9 patients required higher dose of 800mg34. The phase III Intergroup trial proved that KIT exon 11-mutant GIST had a better objective response rate (ORR) of 71% and OS of 60 months, versus 45% (p = 0.01) for both exon 9-mutant and KIT/PDGFRA wild-type tumors with OS of 39 and 49 months, (p = 0.049)[35].

The duration of imatinib in metastatic patients is until disease progression. In the French Sarcoma Group trial, 58 patients were randomised to imatinib continuation versus interruption after 1 year of treatment. Most of the patients in the interrupted group progressed, however majority of them responded to reintroduction of imatinib and no difference was seen in OS, resistance patterns or quality of life[36]. Another new TKI called masitinib mesylate is being studied in phase II and III trials which has greater selectivity in exon 11 mutation[37,38].

Resistance to TKI poses a significant challenge in the management of GIST. Imatinib resistance could be either primary (in which the tumor does not show any response to imatinib) or secondary (resistance after an initial period of response). The important mechanisms proposed for imatinib resistance are[39]:

1. Development of secondary mutations in KIT and PDGFRA which are resistant to imatinib75

2. Amplification and over expression of the KIT genome

3. Activation of alternate receptor tyrosine kinases

4. Functional resistance- activation of other sites in the KIT apparatus (other than usual juxtamembrane site)

Response Assessment to Imatinib in GIST

In GIST due to necrosis and cystic degeneration calculation of tumor size may not be accurate, thus decreasing the effectiveness of RECIST. Hence the criteria proposed by Choi et al are preferred[40] (Table 2).

Second Line Therapy for Metastatic GIST

In metastatic GIST patients who have progressed on imatinib or are intolerant to imatinib, sunitinib is recommended as the second line agent. The recommended dose is 50mg once daily for 4 weeks with a 2 week break. Sunitinib acts against both kit and PDGFR receptor. It acts better than imatinib in patients with exon 9 mutations and wild type GISTs. In a phase III trial, the PFS was 24 months versus 6 months for patients on sunitinib versus placebo respectively[41]. In another phase III trial, the PFS with sunitinib was 7, 9 and 13 months in patients who progressed after 1, 3 and 5 years of imatinib respectively[42]. In a study by Demetri et al, sunitinib was compared with placebo (patients on placebo arm could crossover to sunitinib arm on disease

Table 2: Assessing response on tyrosine kinase inhibitor therapy

Response	Choicriteria	RECIST criteria
Complete response (CR)	1. Disappearance of all lesions 2. No new lesions	Same
Partial response (PR)	1. A decrease in size of 10 % or more or a decrease in tumor density (HU) of 15% or more on CT 2. No new lesions 3. No obvious progression of non measurable disease	At least a 30% decrease in the sum of diameter of target lesions
Stable disease (SD)	1. Does not meet criteria for complete response, partial response, or progression 2. No symptomatic deterioration attributed to tumor progression	Same as 1
Progression (PD)	1. An increase in tumor size of disease 10% or more AND does not meet criteria of partial response by tumor density (HU) on CT 2. New lesion 3. New intra tumoral nodules or increase in the size of existing intra tumoral nodules	1. At least a 20% increase in the sum of diameter of target lesions, along with an absolute increase of at least 5 mm 2. New lesions

progression). Although there was no significant difference in OS due to crossover, TTP was 27 weeks in the sunitinib arm versus 6 weeks in the placebo arm. Patients in the placebo arm had a 3 fold greater risk of disease progression (HR 0.339; 95% CI, 0.244-0.472; pd" 0.001)[43]. The toxicity seen with sunitinib is fatigue, anorexia, stomatitis, diarrhea, hand foot syndrome, thrombocytopenia, hypertension and hypothyroidism[44]. Patients with D842V mutations are resistant even to suntinib.

Third Line Therapy for Metastatic GIST

In patients post progression on imatinib and sunitinib a new TKI called regorafenib has been studied. It is a pan-TKI which has multiple targets: KIT, RET, RAF1, BRAF, VEGFR1-3, TEK, PDGFR and fibroblast growth factor receptor (FGFR)[45, 46]. The dose recommended is 160mg oral tablet once daily for 21 days, with cycle of 28 days each. In the initial phase II study of 3rd line regorafenib, a PFS of 10 months was seen[47]. Phase III GRID study randomized 199 patients to third-line regorafenib versus placebo. On progression, patients in the placebo arm were allowed to cross over to the regorafenib arm. At 3 months and 6 months, PFS was 60% versus 11%, and 38% versus 0% in the regorafenib versus placebo arm respectively. The median PFS was 4.8months versus 0.9months in the regorafenib versus placebo arms respectively (HR 0·27, 95% confidence interval (CI) 0·19–0·39; p <0·0001), whereas the disease control rate was 53% versus 9% (p <0·0001). Due to crossover, OS was not statistically different[48]. Moreover the benefit of regorafenib was less if the patient had received less than 6 months of imatinib. The most common toxicities seen were HFS, mucositis, diarrhea, hypertension and fatigue and many patients required dose reduction (50%), although discontinuation rate was very less (2%). Based on this study, regorafenib as a third-line agent in metastatic GIST received FDA approval in 2013. Like sunitinib, patients whose tumours are positive for D842V mutation are also resistant to regorafenib.

If regorafenib is not feasible, imatinib re-challenge in third-line setting can also be tried, but it has been observed that it is effective only if the tumor initially was imatinib responsive while used in first line. In the phase III RIGHT study, 81 patients were randomized to imatinib re-challenge or placebo as 3rd line agent. The PFS was 1.8 months versus 0.9 months in the imatinib versus placebo arms respectively, without any OS benefit[49]. Sorafenib has also been tried as 3rd line agent in phase II trials[50].

Future Perspective/ Conclusion

Due to development for resistance to imatinib and sunitinib newer drugs are being studied. Nilotinib and ponatinib are the other TKIs which and currently being studied[51, 52, 53]. Heat shock proteins (HSP) prevent the proteosomal degradation of KIT and PI3K/AKT pathway maintains cell survival, hence HSP90 and PI3K inhibitors are under trial[54, 55, 56]. IGF1 receptor inhibitor linsitinib is being studied in wild type GIST, where usually imatinib is resistant. Other drugs which are being studied are m TOR inhibitors (everolimus and temsirolimus), AKT inhibitor (perifosine), CDK inhibitor (flavopiridol), IGF1/BRAF inhibitors and anti-KIT monoclonal antibody called SR1[57]. In PDGFRA D842V mutated GISTs crenolanib, an oral benzimidazole is considered to be a more potent inhibitor of PDGFR[58]. The study of numerous molecules is a hope that GIST patients can have a reasonable survival even in the scenario of imatinib resistance. The Indian Council of Medical Research has published the guidelines/ consensus document for managing patients with GIST and gives a comprehensive review[59].

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<div style="border:1px solid">PERSPECTIVE</div>

A PATHOLOGIST OVERVIEW OF GASTROINTESTINAL STROMAL TUMORS

Introduction

Gastrointestinal Stromal Tumors (GIST) accounts for 1% of all GI malignancies and is the commonest mesenchymal tumor of this organ. It was originally classified with other tumors like Leiomyoma, Leiomyosarcoma, Leiomyoblastoma and Schwannomas as its distinction from them was impossible based on morphology alone, since no immunophenotyping was available then. It is in 1970 that suspicion of GIST being a different entity was raised, based on their lack of tissue specific ultramicroscopic features. Mazur and Clark on the basis of a lack of distinctive IHC & morphological attributes, applied a non committal appellation of "Gastric Stromal Tumors" to this neoplasm. It was the discovery in 1998 (Hirota et.al.), of gain-of-function mutations in the C-KIT proto-oncogene and the over expression of mutated protein, that allowed separation of these tumors into a well defined category of GISTs versus these other histopathological subtypes of GI tumors. Later on (2003), it was noted by Heinrich et al that GISTs can also contain activating mutations of the PDGFRA gene.

On the basis of C-KIT mutations and consequently its over-expression in GIST, the histogenesis of this tumor has been postulated from "Interstitial Cells of Cajal". This is the cell type that needs c-kit protein for differentiation and maturation and is the only cell type in GIT to normally express this receptor protein.

Definition

GIST is defined as a mesenchymal neoplasm that recapitulates differentiation towards interstitial cells of Cajal and has a broad range of biological behaviour from nearly benign to fully malignant based on (i) Anatomic Location (ii) Size (iii) Mitotic activity and (iv) Type and Sum total of "Genetic Alterations". Conceptually all GISTs are taken as Malignant with varying risk of recurrence. Risk stratification is an important aspect of GIST pathology as we shall see in the later part of this paper.

Pathology Reporting

The gross pathology report of a GIST shall include following information:

a. Location
b. Size
c. Mucosal involvement
d. Multifocality: No. of foci
e. Perforation: natural/ iatrogenic
f. Extension to several loops/ adjacent organ
g. Gross involvement of the margin, distance

Table1: Site wise risk of aggressive behaviour

Site	Incidence	Frequency of Aggressive Behaviour
Gastric	60-70%	20%
Small intestine	20-30%	Doudenum - 30%, Rest-50-60%
rectum and Colon	<5%	Colon-All, Rectum-40%
Other (omentum, mesentery, esophagus	<5%	Omentum & Mesentery - 50% Esophagus-All

Location of the tumor is a strong predictor of its biological behavior (Table 1). GIST from stomach are least likely to be aggressive while an aggressive behaviour is expected of larger fraction of small intestinal GIST. Table 2 below displays the risk stratification based on tumor location along with site wise distribution of GIST.

Table 2: Risk stratification of GIST based on location, size and mitotic index

Mitotic Index	Size, cm	Site and Risk of Progressive Disease (%)			
		Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5/50/hpf	≤ 2	None (0)	None (0)	None (0)	None (0)
	>2≤5	Very low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
	>5≤10	Low (3.6)	Moderate (24)	(Insufficient data)	(Insufficient data)
	>10	Moderate (10)	High (52)	High (34)	High (57)
≤5/50/hpf	≤2	None	High	(Insufficient data)	High (54)
	>2≤5	Moderate (16)	High (73)	High (50)	High (52)
	>5<10	High (55)	High (85)	(Insufficient data)	(Insufficient data)
	>10	High (86)	High (90)	High (86)	High (7)

Table 4: IHC panel useful for establishing the diagnosis of GIST

Diagnosis	C-Kit DOG1 PK-CØ	CD34	SMA	DESMIN	SMMH CALDE SMON	S-100	HMB 45	B-CATENIN	ALK
GIST	++	+	±	-	-	±	-	-	-
LM/LMS	-	±	++	±	++	-	-	-	-
Schwannoma	-	-	-	-	-	++	-	-	-
SFT	-	+	-	-	-	-	-	-	-
Melanoma	+(c-kit)	-	-	-	-	++	++	-	-
Fibromatosis	-	-	-	-	-	-	-	+	-
IMT	-	-	-	-	-	-	-	-	+

LM- Leiomyoma, LMS- Leimyosarcoma, SFT- Solitary fibrous tumor, IMT- Inflammatory myofibroblastic tumor

Size is again an important risk stratifying tool along with mitotic activity and previously alluded tumor location. Table 2 below shows, how the aforementioned elements are amalgamated to estimate the risk of recurrence.

Mucosal involvement, multifocality, perforation of tumor both naturally or during surgery, and extension of tumor through several loops of intestine or into adjacent organ are all ominous and should be highlighted in the surgical pathology report. Involvement of margin and distance from margin are also risk assessors for recurrence of tumor.

The microscopic pathology of GIST shall address the following questions. Is it GIST? What is the histological subtype? How much is the mitotic activity? Does the tumor exhibit necrosis and is the status of margin same as assessed on gross examination.

GIST morphology is varied and the tumors exhibit spindle cells (70%), epithelioid cells (20%) and mixed spindle and epithelioid cells (10%) morphology. Tumors can be bland in appearance or be completely bizarre. This extreme variance in appearance invokes a large differential diagnosis which are listed (Table 3)

Table 3: Differential diagnosis in consideration

Spindle cell type	Epithelioid type
Fibromatosis	Melanoma
Leiomyoma, leiomyosarcoma	Epithelioid MPNST
Schwannoma	Epithelioid LMS
Inflammatory fibroid polyp (IFP)	Carcinoma of Unknown Primary
Melanoma	
Inflammatory Myofibroblastic Tumor	

To wrap up a diagnosis of GIST, role of IHC is of paramount importance and a wide array of antibodies is required. Table 3 below enlists the antibodies used in diagnosis of GIST and how these are used to resolve the differential diagnosis.

Necrosis was initially considered a feature of aggressiveness but it is no more so. Reporting necrosis is left to the personal choice of pathologist. However, counting mitosis and counting those correctly is the most crucial of microscopic evaluation and it is here, where most mistakes are made. First thing to remember is that mitotic activity is reported per 50 fields and not the usual per 10 fields. Secondly, the most active fields are chosen. Thirdly, the field areas being different with different makes of microscope, mitotic count is measured in 5 mm2 and reported as "n/50 hpf". In cases, where the mitoses are difficult to see, use immunohistochemistry for pHH-3, a marker for mitoses. Surgical margins of resection are important

Driver mutation GIST
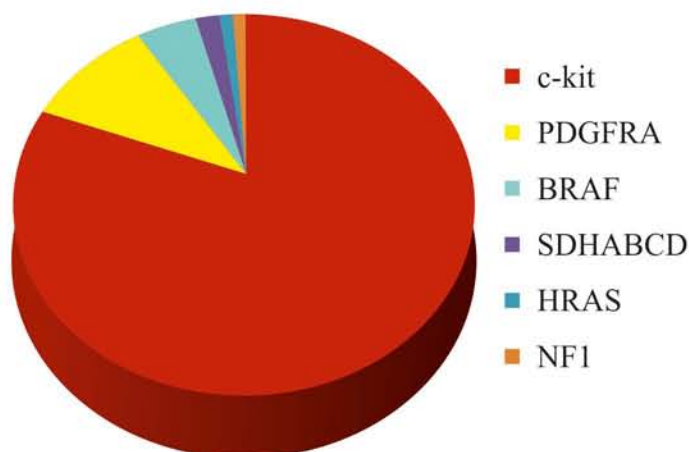
Fig1: Driver mutation in GIST with their relative proportion

- c-kit
- PDGFRA
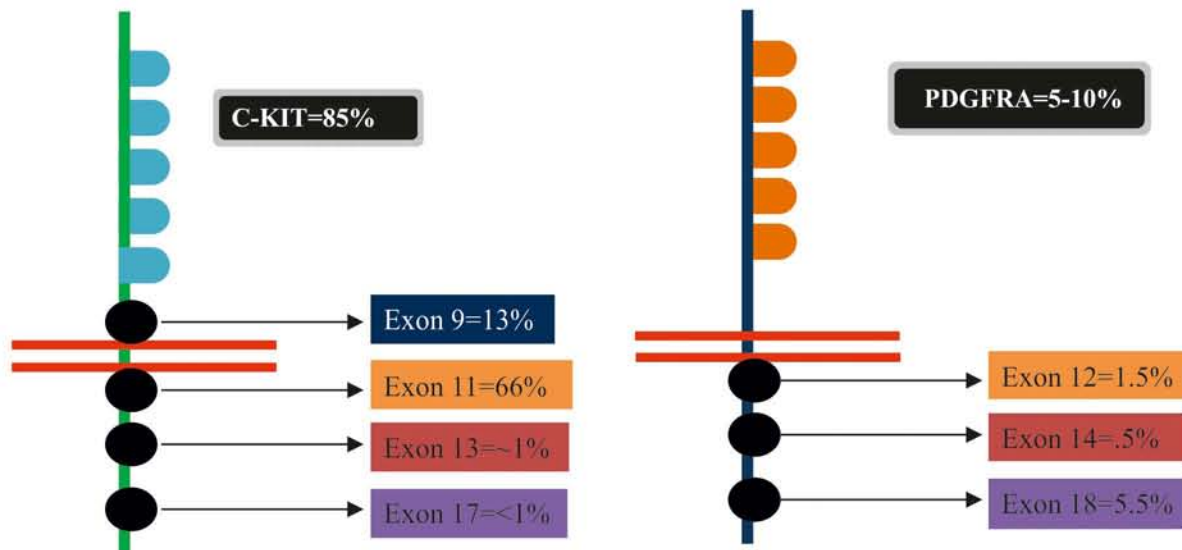- BRAF
- SDHABCD
- HRAS
- NF1

Fig 2: The structure and sites of mutations in C-KIT and PDGFRA genes

to assess the risk of recurrence. Not merely the distal and proximal resection margin but also the surgical margins of mesenteric, omental or retroperitoneal soft tissue is thoroughly assessed.

The pathology report is important to make decision about adjuvant imatinib/ an appropriate tyrosine kinase inhibitor (TKI) use and hence must be meticulously done.

Molecular Biology of GIST

GIST was a malicious tumor unless resected completely with no suitable adjuvant chemotherapy. Demonstration of C-KIT mutations as drivers and their engagement by imatinib and subsequently by other TKI has changed the scenario favorably. The KIT mutation was first described by Hiroto et.al. in a seminal article published in journal "Science" in 1998.

Since, several other drivers with lesser frequency of occurrence have been identified. The Fig1 below enlists the driver mutations identified in GIST and their relative incidence

Activating KIT and PDGFRA mutations, the commoner of the several such mutations in GIST differ in type and affect different receptor sites. It is well known that sensitivity to imatinib depends on the location of the KIT and PDGFRA gene mutation. Based on in vitro studies and subsequent clinical trials, it has been shown that a subset of GISTs harbouring KIT and PDGFRA mutations in the second tyrosine kinase (TK) domain (activation loop domain) do not respond well to imatinib treatment.

C-KIT & PDGFRA are homologous genes forming similar receptors. These tyrosine kinase receptors belonging to family of RTK-III have three domains comprising of (Fig 2):

a. Ligand binding domain which is extracellular and has five loops akin to immunoglobulin molecule
b. A transmembrane region
c. A cytoplasmic domain comprising of a juxtamembrane region and also housing a dual folded tyrosine kinase pocket.

The most mutations occur in C-KIT (~85%). Of these, the great majority happens in region of exon 11(66%). The second commonest C-KIT mutation occurs in Exon 9 and accounts for 13% of C-KIT mutations. Mutations also occur in TK domain of C-KIT corresponding to genetic location in Exon 13 and Exon 17(< 1%). A rare Exon 8 mutation (<1%), especially in "Extra Intestinal Stromal Tumor" has also been described.

PDGFRA has corresponding mutations except in extracellular juxta-membranous portion of the receptor. The location and the frequency of mutations in PDGFRA are shown in Fig 2. The PDGFRA mutations also result in over-expression of C-KIT receptor but, the expression is weak.

Those GISTs which do not reveal either of the two gene alterations are often alluded to as wild type. Some amongst these reveal mutations of IGF1R or BRAF and inactivation of KIT-inhibitor phosphatases leading to uninterrupted C-KIT receptor activity.

Pediatric GISTs and familial GISTs are rare and are associated with germline 'loss of function mutations' in SDH genes responsible for generation of succinate dehydrogenase enzyme. There are also cases reported in literature of familial GIST caused by germline mutations in C-KIT and PDGFRA. Table 4 below outlines the familial and syndromic GISTs.

Table 5: The familial and the syndromic GISTs. This table highlights the clinical and mutational profile, sites involved along with the expected course of disease. Quadruple wild alludes to lack of mutation in any of the C-KIT, PDGFRA, RAS pathway genes or SDH

	Heredity	Mean Age (y)	M/F	Associated Lesions	Mutations	GIST Location	Behavior
Familial	AD	45	M&F	Mast cell lesions, Achalasia	Germline mutations in C-KIT or PDGFRA	Small intestine	Frequently aggressive
Carney-Stratakis	AD	23	M&F	Paraganglioma	Germline mutation in SDH	Stomach Epithelioid type	Metastasize. Protracted
Carney Triad	None	<30	>95%F	Lung chondroma, paraganglioma	Quadruple wild	Stomach epithelioid	Metastasize. Protracted
NF1	AD	40-50	M&F	Neurofibromatosis	Germline mutation in SDH	Small intestine spindled	As for usual
Sporadic SDH-B Deficient (Pediatric Type)	None	<16, rarely also adults	>90%F	None	Quadruple Wild (Phenotypically SDH deficient but lack genetic alteration(s)	Stomach epithelioid	Metastasize. Protracted. May go to nodes

Role of Molecular Features and Tumor Biology

The molecular alterations of GIST provide a tool for diagnosis, prognosis and prediction of response to a TKI. Let's now see these benefits of mutational analysis.

Diagnosis: There are always cases which are difficult to diagnose because of varied morphology or conflicting immunohistochemistry. However, these cases can draw benefit from an appropriate TKI if the diagnosis is properly established. If we look at the long list of previously alluded differential diagnosis (Table 3); it becomes clear that demonstration of C-KIT mutation will limit the diagnosis to GIST and Melanoma (Melanoma can harbor C-KIT mutation in a small fraction of cases). The latter can be separated out from GIST by using IHC for Melan A and Sox10.

Prognosis: Are there mutation subtypes which portend poor prognosis? NCCN guidelines are silent on value of mutational typing to assess prognosis. ESMO admits some genotypes have a distinct natural course but has not committed on performing mutation analysis for this reason. However, independent literature- suggests such association eg.

- Exon 11 deletions portend poor outcome unless treated by imatinib. Exon 11 del 557/558 has also been shown to have poor outcome with a 3 fold increased risk of recurrence in first 4 years.
- PDGFRA mutations have a favourable prognosis with a lower risk of metastasis.
- Two studies showed that 80% of tumors containing PDGFRA Exon 14 and 18 mutations with a low/absent mitosis (<5/hpf) and epithelioid morphology are largely (95%) of gastric location with superior prognosis.

Table 6: Effects of C-KIT and PDGFRA mutations in GIST

Summary of Effects of "Molecular mutations in C-KIT"	

KIT gene (type 3 RTK)	**Characteristics**
	 • Primary Mutations cluster most commonly on exon 11: less commonly on Exons 9, 13 and 17
	 • Acquired mutations occur during TKI treatment on exons 13, 14 and 17
	 • Acquired Mutations decrease binding capacity of TKI is
	 Therapeutic implications
	 • Exon 11 mutation
	    • Associated with TKI sensitivity
	 • Exon 13 mutation
	    • Primary (non-therapy associated) - TKI sensitive
	    • But, secondary (therapy induced) - TKI resistant
	 • Exon 9 mutation
	    • Requires escalated dose of TKI for response
	    • Better response to sunitinib than imatinib
	 • Exon 17 mutation
	    • primary - TKI sensitive
	    • D816 V (exon 17) - TKI resistant
	    • Secondary - associated with TKI resistance

Summary of effects of "Molecular mutations in PDGFRA"	

PDGFRA (Type III RTK)	**Characteristics & Therapeutic implications**
	 • Mutations cluster on Exons 12, 14 and 18
	    • Exon 18 most common - D842V and D846 V mutation
	    • D842 V is completely resistant

Predictive value: Do mutation subtypes predict response/ resistance to imatinib or any other specific TKI? The answer is an emphati yes and the predictive value of mutation subtype is fairly well established. Kit Exon 11 mutations are highly sensitive to imatinib. Kit Exon 9 mutations are relatively less sensitive and require higher dose of imatinib and a dose of 800 mg against a usual dose of 400 mg has been recommended in some literature. It has also been observed that Exon 17 mutations in C-KIT gene & Exon 18 mutations in PDGFRA; especially D842V are resistant to TKIs. Furthermore, it has been reported that WT-GIST have 8 fold risk of primary progression on Imatinib compared to Exon 11 mutations.

Primary resistance to imatinib has been correlated to the mutation subtype with rate of primary resistance being 5%, 16% and 23% in Exon 11, Exon 9 & WT respectively.

In regard to acquired mutation following exposure to imatinib, the rate of such mutations is highest in Exon 11 mutations and occurs in Exon 13, 14 and 17.

Table 5 summarizes the biology of tumor in accordance with the mutation subtypes noted in most frequently affected C-KIT gene and PDGFRA.

The one last question that begs an answer and is frequently raised is "Shall molecular testing be done in all cases"? My answer will be 'Yes', except < 2 cm gastric GIST which has 0% risk of recurrence. The reasons for saying so are as under:

a. Increased dosage for Exon 9 mutations
b. Complete resistance of D842V- PDGFRA
c. Other resistant mutations in TK2 loop well known
d. Wild type GIST-Response to Imatims is unlikely. therefore use of sumtinib upfront is recommended
e. Knowledge of Base line mutation - shall help separate out the secondary mutations easily.

Conclusion

To conclude, it can be said safely that great advances in diagnosis and management of GISTs have been made in the past decade with extensive use of imatinib in both neoadjuvant and adjuvant settings. This has really converted a hopeless situation to a relatively cheerful one. This entails a correct diagnosis of GIST. The role of IHC in this regard cannot be overemphasized. A validated set of IHC as mentioned before is essential and laboratories reporting on GIST must participate in a good EQAS Program. Adoption of molecular diagnostics in GIST has become essential for best evidence based practice as subtypes determine prognosis and use of TKIs.

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ESMO CLINICAL PRACTICE GUIDELINES FOR GASTROINTESTINAL STROMAL TUMORS

Incidence

Gastrointestinal stromal tumors (GISTs) are rare tumours, with an estimated unadjusted incidence of around 1/100000/year. This only covers clinically relevant GISTs, since it is likely that a much higher number of microscopic lesions could be found pathologically, if looked for. The median age is around 60–65 years, with a wide range. Occurrence in children is very rare, although paediatric GIST represents a distinct subset. Some syndromes linked to GISTs are: Carney-triad syndrome, Carney-Stratakis syndrome, Neuro-fibromatosis type 1.

Diagnosis

When small oesophago-gastric or duodenal nodules <2 cm in size are detected, endoscopic biopsy may be difficult and laparoscopic/laparotomic excision may be the only way to make a histological diagnosis. The standard approach to rectal (or recto-vaginal space) nodules is biopsy/excision after ultrasound assessment, regardless of the tumor size, because the risk of a GIST at this site is higher and the local implications for surgery are more critical. Multiple core needle biopsies is the method of choice. They should be obtained through endoscopic ultrasound guidance, or through an ultrasound/computed tomography (CT)-guided percutaneous approach.

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry, the latter being positive for CD117 and/or DOG1 . A proportion of GISTs (in the range of 5%) are CD117-negative. The mitotic count has a prognostic value and should be expressed as the number of mitoses on a total area of 5 mm2 (which replaces the former 50 high-power field area). Mutational analysis for known mutations involving KIT and PDGFRA genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117/DOG1-negative suspect GIST). In KIT/PDGFRA wild type (WT) GIST, immunohistochemistry for SDHB is done.

Stage Classification and Risk Assessment

The TNM classification has several limitations and its use is therefore not recommended. Prognostic factors are the mitotic rate, tumor size and tumour site (gastric GISTs have a better prognosis than small bowel or rectal GISTs). Tumor rupture is an additional adverse prognostic factor and should be

recorded, whether it took place before or during surgery. Mutational status has not been incorporated in any risk classification at the moment, although some genotypes have a distinct natural history, and, above all, KIT/PDGFRAWT GISTs have peculiar clinical presentations and course.

Staging Procedures

Staging procedures take into account the fact that most relapses affect the peritoneum and the liver. Contrast-enhanced abdominal and pelvic CT scan is the investigation of choice for staging and follow-up. Magnetic resonance imaging (MRI) may be an alternative. For rectal GISTs, MRI provides better preoperative staging information. Chest CT scan or X-rays and routine laboratory testing complement the staging work-up of the asymptomatic patient. The evaluation of fluorodeoxyglucose (FDG) uptake using an FDG-positron emission tomography (PET) scan, or FDG-PET–CT/MRI, is useful mainly when early detection of the tumor response to molecular-targeted therapy is of special interest. Now-a days, it is being routenly used in staging workup.

Treatment

Multidisciplinary treatment planning is needed.

Localised Disease

The standard treatment of localised GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes. R0 excision is the goal. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival and OS advantage . There is consensus that PDGFRA D842V-mutated GISTs should not be treated with any adjuvant therapy, given the lack of sensitivity of this genotype both in vitro and in vivo . Also patients with tumor rupture during surgery should be considered for imatinib therapy as they are at a high risk of peritoneal relapse.

If R0 surgery is not feasible, pre-treatment with imatinib is standard. Following maximal tumour response, generally after 6-12 months, surgery is carried out. Mutational analysis is crucial because it helps to exclude less sensitive or resistant genotypes (e.g. PDGFRA D842V mutations) from therapy with imatinib and allows the use of proper dosing for KIT Exon 9 mutations.

Metastatic Disease

In locally advanced inoperable and metastatic patients, imatinib is the standard treatment, even if the patient previously received the drug as adjuvant therapy without relapsing during it. Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression, even when lesions have been previously surgically excised.

Close monitoring of the tumor response should be carried out in the early phases of treatment since the risk of secondary progression persists over time. Dose escalation is particularly useful in the case of a KIT Exon 9 mutated GIST (if a higher dose was not selected from the beginning), possibly in the case of changes in drug pharmacokinetics over time, or perhaps in the case of some molecular secondary alterations. After confirmed progression on sunitinib, a standard for third line targeted therapy, regorafenib is now routinely available.

Response Evaluation

Both tumour size and tumour density on CT scan, or consistent changes in MRI or contrast-enhanced ultrasound, should be considered as criteria for tumor response. An FDG-PET scan has proved to be highly sensitive in early assessment of tumor response and may be useful in cases where there is doubt, or when early prediction of the response is particularly useful (e.g. preoperative cytoreductive treatments). The absence of tumour progression at 6 months of treatment also amounts to a tumor response.

Follow-Up

Relapses most often occur to the liver and/or peritoneum. The mitotic rate likely affects the speed at which relapses take place. Risk assessment based on the mitotic count, tumor size and tumour site may be useful in choosing the routine follow-up policy. High-risk patients generally have a relapse within 1–3 years from the end of adjuvant therapy. The optimal follow-up schedules are not known. In some institutions, high-risk patients undergo a routine follow-up with an abdominal CT scan or MRI every 3–6 months for 3 years during adjuvant therapy (with a tighter clinical follow-up due to the need to manage the side-effects of adjuvant therapy), unless contraindicated, then on cessation of adjuvant therapy every 3 months for 2 years, then every 6 months until 5 years from stopping adjuvant therapy, and annually for an additional 5 years. For low-risk tumors, the usefulness of a routine follow-up is not known; if selected, this is carried out with abdominal CT scan or MRI, every 6–12 months for 5 years. Very low-risk GISTs probably do not deserve routine follow-up, although one must be aware that the risk is not nil. X-ray exposure is a factor to take into account, especially in low-risk GIST, with abdominal MRI being an option as an alternative.

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PERSPECTIVE

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PET-CT IN GASTROINTESTINAL STROMAL TUMORS

Introduction

It is well known that in sarcomas, including gastrointestinal stromal tumors (GISTs) may not change in size in response to therapy and therefore traditional anatomic tumor response criteria, such as the World Health Organization (WHO) criteria and the Response Evaluation Criteria in Solid Tumors (RECIST), are not as useful for these tumor types as they are for other tumor types. Fortunately enough these tumors mostly show high metabolic activity related to intense glycolysis. Hence positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (18F-FDG) can be used to evaluate these tumors and the response to therapy. It has been seen in various studies that patients of GIST treated with imatinibmesylate the responses evaluation criteria as seen on 18F-FDG-PET are closely related to clinical benefit. It has also been seen that conventional objective response criteria based on tumor size, as measured by computed tomography (CECT), are appreciated at a much later date after the 18F-FDG-PET imaging results prompting the clinicians to take decisions based on the functional criteria. The 18F-FDG-PET response is characterized by a marked decrease in the glycolytic metabolism of GISTs in all patients who respond to imatinib and is appreciated by decrease in metabolic activity in the scan. This response is generally seen 1 month after initiation of therapy, and can also be appreciated as early as 24 hours after treatment begins as reported in few studies. Tumor response to therapy in GISTs, isthus best monitored by using both PET and CT which plays a complementary role and can now very well be done with the current hybrid systems facilitating both anatomic and functional tumor evaluation. 18FDG-PET scanning is effective in staging and restaging GISTs, and for evaluating therapeutic response to a variety of treatments.

Baseline 18F-FDG-PET Study

PET is a functional imaging study that can evaluate tumor metabolism over time. A baseline scan should always be obtained prior to initiating treatment to establish the glucose metabolism in the tumor. A baseline evaluation helps in establishing a denominator against which future studies & quantitative measurements, such as the standardized uptake value (SUV) and total lesion glycolysis (TLG) can be compared. This denominator is essential for characterizing and comparing the metabolic responseand lately the metabolic tumor volume (MTV) when using the European Organization for Research and Treatment of Cancer (EORTC) criteria, which are based on the magnitude of the change in SUV as compared to baseline.

Response Evaluation

18F FDG-PET may be used to detect both short and long-term tumor responses that may not be apparent with anatomical imaging. As mentioned earlier, 18F-FDG PET responses can be observed as early as 24 hours after a single dose of imatinib. However a 25%-30% decrease in SUV max as compared to baseline can be seen within one month of starting imatinib therapy in all GIST patients who appears to be responding to the drug. On the other hand, even when a patient benefits from treatment, it may take weeks, months, or even years for these tumors to shrink anatomically. Importantly, 18FDG-PET scans performed soon after treatment begins may identify patients with primary resistance to the drug who may not benefit from this therapy, and for whom alternative treatment may be required.

Prediction of Outcome

In the pivotal trial of imatinib in metastatic GIST, it was reported that patients who achieved an absolute value for SUVmax of d"2.5 in the tumors 1 month after startingtreatment fared much better than patients who did not [5].The EORTC guidelines for the use of 18FDG-PET as a biomarker of response suggest that a 25% reduction in SUVmax should be considered as the threshold for partial metabolic response (PMR) [7]. Conversely, response at 1 month by the standardized Southwest Oncology Group (SWOG) criteria, was not predictive of outcome [10]. The results in a comparable group of patients imaged 2 months after beginning imatinib therapy, indicated that PMR was also predictive of outcome atthat time point [11] A pilot study in the patient population that participated in the pivotal imatinib trial and was evaluated 1month following initiation of treatment aimed at optimizingresponse criteria and assessing their predictive values using outcome analysis [12] found that an absolute value forSUVmax of 3.4 and a 40% reduction in SUVmax were morepredictive of time-to-treatment failure (TTF) than the 2.5SUVmax threshold and the 25% reduction (PR). However, patients who had stable disease (SD), asdefined by a <50% reduction in the tumour size had significantly better outcomes than patients who experienced growth intheir tumor masses (p < .00005). 18F FDG PET has also been very helpful in resolving ambiguous findings on CT. PET helps in characterization of new lesions which may come up during the course of imatinib therapy in a known case of liver metastasis. Traditional

response criteria, such as WHO, or RECIST, wouldlabel the appearance of these lesions as disease progressioneven if there is regression in the index lesions, than as response to therapy and hence such pattern recognition is important. Isodense lesions in the liver parenchyma may have a change in density post treatment and may become hypodense. Presence or absence of metabolic activity is crucial to differentiate these lesions.The newly proposed CT response criteria use either no growth in tumor size [12] or a combination of tumor densityand size criteria [15] to assess the response of GIST patientsto imatinib, and have shown predictive values regarding time to treatment failure.

Use of 18FDG-PET to Detect SecondaryResistance

18F-FDG PET can aid in the identification of secondary resistance. It has been observed that GISTpatients who originally respond to imatinib, as demonstratedby the inhibition of glycolytic activity soon afterstarting the drug, may exhibit re-emergence of metabolicactivity consistent with clonal de-differentiation and secondary resistance within the original mass.Stopping imatinib therapy in patients with imatinibrefractory GIST can also result in a "flare" phenomenon. Differential response by 18F-FDG-PET,suggest more than one mutation. In that scenario, patients could potentiallyremain on imatinib therapy if it still inhibits metabolic activityin portions of their tumor mass, and receive a new molecularlytargeted drug directed toward the resistant clones.The results also suggest that 18FDG-PET could become anextremely useful functional noninvasive test to tailor treatmentby defining whether a new drug is able to inhibit the re-emerging glycolytic activity seen in the resistant clones.

Role of Hybrid Imaging

Contrast-enhanced CT has conventionally been the method of choice and will continue to play an important role in the management of patients with GIST. However, it is also clear that 18FDG-PET has been and continues to be instrumental to the success story of the molecularly targeted drugs that are now being used to treat this disease. The integration of anatomic and functional imaging in the combined hybrid PET/CT scanner setting maximizes the benefits of each system and demonstrates their complementarities. This combined imaging approach optimizes the diagnostic and treatment plans for patients with GIST and has shows greater sensitivity, specificity, and accuracy in the staging and restaging of patients with GIST. This one stop shop approach may ultimately, and cost-effectively, shorten clinical trials and accelerate drug development.

Conclusion

Metabolic response by 18F FDG PET clearly precedes anatomic response in patients of GIST treatedwith molecularly targeted drugs, and predicts outcome. There is, therefore a compelling need to integratediagnosis and evaluation of patients with GIST and to use 18F FDG PET in the design, testing, and implementation of new drugs and clinical trials in GIST. The lessons we have learned throughout the GIST experience have created many new paradigms with respect to the role of imaging. These new paradigms help todefine and refine the concept of personalized medicine, and already serve as a new basis on which to evaluate newmolecularly targeted drugs in other cancers as well.

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