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Review

CURRENT KNOWLEDGE OF GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tümörlerde güncel bilgiler

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ABSTRACT

Gastrointestinal stromal tumors (GIST), the most common mesenchymal tumors of the gastrointestinal tract, are immunohistochemically and ultrastructurally different from other mesenchymal tumors. They can occur anywhere in the GI tract, commonest site being stomach. GIST occurrence is not restricted to bowel but can involve unusual sites also. The diagnosis and treatment of GIST has been revolutionized over the past decade. The mainstay of treatment remains surgical resection with adequate margin. Though, these tumors are refractory to conventional chemotherapy or radiotherapy but show a good response to molecularly targeted therapy with tyrosine kinase inhibitor. So, in cases where tumor has malignant potential, adjuvant treatment with tyrosine kinase inhibitor may prevent or delay relapse. This review summarises the current clinical and immunohistochemical knowledge of GIST and its treatment.

Key words: Gastrointestinal stromal tumors, C-KIT, PDGFRA, and Imatinib.

ÖZET

Gastrointestinal stromal tümörler (GIST) gastrointestinal traktüsün en sık görülen mezenkimal tümörleri olup, immünhistokimyasal ve ultrastrüktürel olarak diğer mezankimal tümörlerden farklılıklar gösterirler. Gastrointestinal sistemde herhangibir yerde görülmekle beraber en sık midede görülürler. GIST'ler pasajı tıkamaktan çok, sıradışı yerlerde yerleşim göstermeye eğilimlidirler. Son on yılda tedavisi konusunda devrim niteliğinde gelişmeler olmuştur. Esas tedavi tümörün yeterli miktarda sağlam doku ile birlikte cerrahi olarak çıkarılmasıdır. Bu tümörlerin kemoterapi ve radyoterapiye dirençli oldukları bilinmekle beraber, özellikle tirozin kinaz inhibitörleri ile yapılacak moleküler tedavilerden başarılı sonuçlar alınmaktadır. Cerrahi tedavi ve tirozin kinaz inhibitörleri ile yapılan adjuvan tedavi günümüzde hastalığın nüksünü önleyebilmekte veya geciktirmektedir. Bu makalede, GIST'lerin klinik ve immünhistokimyasal özellikleri güncel bilgiler ışığında gözden geçirilmiştir.

Anahtar kelimeler: Gatrointestinal stromal tümörler, C-KIT, PDGFRA ve İmatinib.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) represent 1% of all GI malignancies and it is the most common type of mesenchymal neoplasm of GI tract. GIST can be defined as specific, typically CD 117 positive and C-KIT or platelet derived growth factor receptor (PDGFR) mutation driven mesenchymal tumors (1,2). Stromal means they develop from tissues that support the connective tissue controlling the movements of the gut. They arise from interstitial cells of cajal (ICC), the GI pacemaker cells (1), present in and around the myenteric plexus, act to coordinate gut peristalsis by linking the smooth muscle cells of bowel wall with the autonomic nervous system.

Earlier they were classified as smooth muscle or nerve sheath tumor. They were labeled as leiomyomas or leiomyosarcomas because of their histologic resemblance to smooth muscle neoplasms, but they were noted to be exceptionally resistant to standard chemotherapy regimens to leiomyosarcomas arising from other sites respond well. They were also noted to lack the characteristic muscle antigens (SMA, desmin, cytokeratin) that defined leiomyo-

sarcomas. S-100 and NSE could not be demonstrated. These tumors expressed CD-34 antigen (this is an antigen which is shared between hematopoetic stem cells as well as vascular and myofibroblastic cells), but CD-34 positivity characterized only 50% of GIST and a good proportion of smooth muscle and schwann cell tumors could express CD34, so CD34 is neither sensitive nor specific for GIST.

The term stromal tumor was introduced in 1983 by Mazur and Clark (3). Till 1999 diagnostic criteria for GIST remained controversial. From 1999,CD117 positivity became definitional for GIST. CD117, a the product of C-KIT gene, is expressed among normal interstitial cells of cajal (ICC), mast cells, melanocytes, a variety of epithelial, fetal endothelial cells. CD117 may be negative in 2-5% of GISTs. CD117 is sometimes lost in metastasis.

CLINICAL FEATURES

GIST affects most commonly middle aged or older individuals (50-60 years) but may arise as congenital tumor (4) or in children (5). Most tumors are sporadic in nature and also occurs as a component of three hereditary syndromes;

Neurofibromatosis-1 (NF-1); affected patients have a deficiency of neurofibromin protein and clinically patients will have café-au-lait spots, freckling, neurofibromas, malignant peripheral nerve sheath tumors, ganglioneuromas and GIST. GIST in NF-1 tends to be multiple, typically involving small intestine, and lack PDGFR and C-KIT mutation (6).

Familial GIST; includes GIST, hyperpigmentation, urticarial pigmentosa, mastocytosis, dysphagia and hyperplasia of ICC (7).

Carney's triad; includes gastric GIST, paraganglioma, and pulmonary chondroma. GIST occurs in young (<20years) individuals, shows a strong female predominance, and are multifocal, epitheloid with low risk of metastasis (8,9). GIST also complicates tuberous sclerosis or following radiation therapy.

Most commonly affected organ is stomach (60%), followed by ileum and jejunum (30%), duodenum (5%), colorectum (<5%), esophagus and appendix (very few reported cases). Extra GI stromal tumors (6%) involves mesentery, omentum,peritoneum and retroperitoneum. Benign GIST may be asymptomatic in contrast, malignant tumors are rarely asymptomatic. Most common symptoms are abdominal mass, GI bleed and abdominal pain. Others symptoms like nausea, vomiting and weight loss may be present. In most patients, the detection of GIST is during evaluation of non-specific symptoms. Usually symptoms tend to arise only when the tumors reach a large size or are in critical anatomic localization (e.g. constricting gastric outflow. 2/3rd of GISTs exceed 5 cm in diameter at presentation, this may be because GISTs grow by displacing adjacent structures rather invading them.

DIAGNOSIS

Pathology

GISTs vary in size from 1-45 cm. They can be submucosal, intramuscular or subserosal, although most are centredaround the submucosa or muscularispropria. They are usually well marginated, surrounded by a thin pseudocapsule of compressed normal tissues, can be solid or cystic and appear as single nodules, plaques, or multinodular lesions, with variable haemorrhage/ necrosis, including mucosal ulceration and tumor cavitation. The tumors grow in an endocentric or exocentric fashion. Tumors with both endocentric and exocentric growth patterns have a dumbbell shape. On cut section, GICTs lack the bulging, whorled cut surface characteristic of smooth muscle tumors.

Histologically, they have spindle, epitheloid and pleomorphic forms, 70% of gastric and most intestinal GIST are spindled (10). A minority of GIST (20%) shows focally incomplete features of smooth muscle differentiation and some shows neuronal like differentiation.Histologic variants of GIST are- gastrointestinal autonomic nerve tumors (GANT), signet ring cell variant, mesothelioma like GIST variant, oncocytic variant, small cell variant and cytotoxic T- lymphocyte rich GIST.

Radiologic features

Radiologic features are not specific, but most large mural gastric masses are GISTs. CT is useful to assess the extent of the primary disease and the presence of metastatic disease. MRI may provide further soft tissue delineation. PET with the tracer 18- FDG demonstrates intense uptake, but may not distinguish GIST from other malignancies. Its main use is in demonstrating the presence or absence of metastases.

Endoscopy

Gastric tumors are often detected by endoscopy. Smaller tumors are usually treated by excision biopsy. For larger lesions, the use of preoperative biopsy is controversial because there is risk of tumor rupture, hemorrhage, and perforation of viscera. The diagnostic yield from endoscopic biopsy is approximately 50%.

Immunohistochemistry

GISTs are positive for CD 117 antigen (which is an epitope for the KIT receptor tyrosine kinase), DOG 1, CD 34, variable actin, S-100 protein, and PDGFRA. CD 117 is positive in vast majority of benign and malignant GISTs, though it may be negative in 2-5% of GISTs. CD 34 is positive in 40-100% of GISTs, and its expression varies with location within the GI tract with maximum positivity in esophageal GISTs. Tumors that are CD34 positive are almost always CD 117 positive, and most CD 34 negative tumors are CD117 positive. CD117 is sometimes lost in metastasis.

Molecular testing

Most mutations in C-KIT are in exon 11, and most mutations in PDGFRA in exon 18. Some of the mutations are predictive of response to targeted therapy. Gene expression patterns in GISTs are assessed by DNA microarray techniques. The technique revealed that the gene FLJ10261 responsible for encoding the DOG 1 protein is specifically expressed in GISTs, irrespective of KIT or PDGFRA mutation status. However, its function is not well understood, although it seems to be fairly specific to GIST and rarely being expressed in other soft tissue tumors. In future it may play a pivotal role in diagnosis of GISTs, especially in PDGFRA mutants failing to express the KIT antigen (11).

Fine needle aspiration biopsy

FNAB can be used to diagnose GISTs with appropriate immunohistochemistry but cannot be used to assess malignant potential

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes;

1. Leiomyoma, leiomyosarcomas (SMA, desminpositive, negative for CD117 and S-100 protein, usually negative for CD34),

2. Schwannomas (S-100 protein positive, may be positive for CD34, negative for CD 117 and negative muscle markers) and

3. Fibromatosis (90% positive for nuclear beta-catenin, may be positive for actin, most lack desmin, spurious CD117).

BEHAVIOUR AND PROGNOSIS

Perfect separation of malignant and benign GISTs cannot be achieved. However, the main prognostic factors identified have been mitotic count and tumor size (12) and other factors are site and age, mucosal invasion, presence of metastasis, necrosis, cytologicatypia, nature of the stroma, KIT or PDGFRA mutational status, cytomorphology, loss of heterozygosity at 1p36. Guidelines using combinations of maximum dimension and mitotic count for defining risk are given in Table 1. They often metastasize to abdominal cavity and liver, rarely to bone, soft tissue, skin, lymph nodes and lungs. Metastasis can occur than 10 years after follow up, so there is a need of long term follow up.

Esophagus; GISTs account for a minority of esophageal stromal tumors (and leiomyomas for the majority) and involve the lower third or gastroesophageal junction, predominantly in males. All are CD117 and CD34 positive, and about 15% have SMA or desmin. The majority are malignant. Size more than 10 cm is a poor prognostic factor and median survival for esophageal GISTs is 29 months.

Stomach; The consensus is that 5 mitoses per 50 high power fields (hpf) and size greater than 5 cm are adverse prognostic factors (13). The 5 year survival rate for gastric GISTs is 80%, with improvement in completely resected cases (Table 2). There is no evidence that radical surgery improves survival, so the least extensive surgical procedure compatible with complete excision is advisable. Gastric GISTs are more frequent in males. About 20-25% of gastric GISTs are malignant. Large tumors in the fundus or cardiac area and posterior wall are more likely to be malignant.

Table 1: Proposed guidelines using combinations of maximum dimension and mitotic count for defining risk (12).

	Size (cm)	Mitotic Count/50 hpf
VLR	<2	<5
LR	2-5	<5
IR	<5 5-10	6-10 <5
HR	>5 >10 Any	>5 Any >10

VLR; very low risk, LR; low risk,
IR; Intermediate risk, HR; High risk,
hpf- high power field

Duodenum; GISTs are more common in the second part, and 35-50% are malignant. 5 mitoses per 50 hpf and size greater than 5 cm are poor prognostic factors.

Jejunum and ileum; GISTs are most aggressive. About 40% result in patient deaths. These GISTs can be spindled, epitheloid or mixed; mixed and epitheloid tumors are associated with worse behavior than spindled tumors. The presence of skeinoidfibres,PAS reactive thick collagen fibres, present in about 45% of cases, is a favourable prognostic factor. As in other sites, the most important factors determining the prognosis are tumor size and mitotic index. GISTs of the jejunum and ileum treated surgically have been shown to have a 39 % tumor related mortality, which was twice that of gastric GISTs (14,15). Large (>10 cm), mitotically active (>10 mitoses/50 hpf) are highly aggressive (Table 3,4).

Colon; Tumors are most common in adults in 6th decade of life in the ascending and descending colon and usually present with pain or mass. They are typically transmural tumors with intraluminal and outward- bulging components. A size of 5 cm and 5 mitoses per 50 hpf is considered as threshold for malignancy.

Appendix; GISTs of the appendix are rare. Only 4 cases have been reported in the literature. All four were spindle cell tumors.

Anorectal; GISTs are rare, most arise within the muscularispropria. They are generally a homogenous group of cellular tumors composed predominantly of spindle cells; skeinoidfibres are absent. Small submucosal lesions without mitoses and pleomorphism behave in a benign fashion.

Extragastrointestinal GISTs; Extra GI GISTSs are extremely rare, more commonly GISTs in these locations represents intra-abdominal metastases from gastric or intestinal primaries. Search of origin of primary tumor whether it is from stomach or intestines is always necessary for apparent extra-GI GISTs. The imaging appearance of mesenteric and omental GISTs is indistinguishable from that of other sarcomas that may arise in these locations.

Table 2: Suggested guidelines for assessing the malignant potential of gastric gastrointestinal tumors of different sizes and mitotic activity (13).

Benign (no tumor related mortality detected) • Group 1 (≤2 cm, ≤5 mitoses/ 50 hpf)
Probably benign (very low malignant potential, < 3% PD) • Group 2 (>2 and ≤ 5 cm, ≤ 5 mitoses/ hpf) • Group 3a (>5 and ≤ 10 cm, ≤ 5 mitose/ hpf)
Uncertain or low malignant potential (no PDs but too few cases to reliably determine prognosis) • Group 4 (≤ 2 cm, > 5 mitoses/ hpf)
Low to moderate malignant potential (12%-15% tumor-related mortality) • Group 3b (>10 cm, ≤5 mitoses/50 hpf) • Group 5 (>2 and ≤5 cm, >5 mitoses/ 50 hpf)
High malignant potential (49%-86% tumor-related mortality) • Group 6a (>5 and ≤10 cm, >5 mitoses/ 50 hpf) • Group 6b (>10 cm, >5 mitoses/ 50 hpf)
Hpf; high power field, PD; Progressive disease.

Table 3: Miettinen classification of small intestinal GISTs (14).

Group	Size (cm)	Mitoses (per 50 hpf)	Prognosis
1	≤2	≤5	Generally behave in benign fashion
2	>2-5	≤5	6% develop metastases and die of their disease
3	>5	≤5	31% develop metastases; median survival 18 months
4	≤2	>5	There were no tumors in this group
5	2-5	>5	50% risk intra-abdominal spread, metastasis or death
6	10	>5	86% intra-abdominal spread or metastasis

Table 4: Prognosis of gastric versus small intestinal GISTs (15).

Stomach GISTs		Small Intestinal GISTs;	
Size (cm), Mitoses (per 50 hpf)	Outcome (with metastases)	Size (cm), Mitoses (per 50 hpf)	Outcome (with metastases)
<10, <5	3%	<5,<5	3%
>10, ≥5	86%	>10,≥5	86%
>10, <5	11%	>10,<5 or <5, ≥5	>50%
<5, ≥5	15%	5-10, ≥5	24%
20% (Ttumor-related deaths)		40% (Tumor-related deaths)	

MANAGEMENT

Surgery;

Surgery is the standard initial management for all localized GISTs. The tumor should be removed en-bloc, with a clear margin. The pseudocapsule should be removed and not penetrated. Therefore, a wedge resection (stomach) or segmental resection (intestine) is required. If neighboring structures are involved, en-bloc resection should still be contemplated. The optimum surgical margin has not been clarified. Despite radical resection with clear margins, 40-80% recurs in the abdominal cavity. However, the majorityof recurrences are solitary and thus may be resectable. Lymph node dissection or biopsy is not recommended as lymph node metastases are very rare. More recently, there has been a move to laparoscopic surgery, particularly for gastric GISTs. Spontaneous tumor rupture or rupture during surgery increases the risk of peritoneal recurrence and is an adverse prognostic factor. Most recurrences occur within 2 years of resection. In a series of 200 GISTs, median survival was 66 months for complete resection compared with 22 months for incomplete resection or unresectable disease (16). Surgery does not play significant role in metastatic GIST because most metastases are multiple hepatic metastases or multiple sites of intra-abdominal metastatic disease.

Chemotherapy;

The efficacy of chemotherapy is very low, with response rates less than 10%. Mechanisms responsible for extreme resistance to chemotherapy are;

1. Increased levels of glycoprotein (the product of multidrug resistance-1 gene),
2. Presence of multidrug resistance protein.

These cellular efflux pumps may prevent chemotherapy from reaching intracellular therapeutic concentration in the target GIST cells.

Radiotherapy;

Radiation therapy (RT) rarely plays any role in management of GIST. RT plays palliative role;

1. Targeting RT with newer techniques like intensity modulated RT or proton beam irradiation might be used for palliation in patients suffering from focal bleeding from a specific site of GIST recurrence.
2. For pain control in patients with liver metastases or large metastatic lesions fixed to the wall of the abdomen or pelvis.

Hepatic artery embolization; This technique may provide palliation in patients with GIST metastatic to the liver. Due to the vascular nature of GIST, occluding the supplying artery may be effective.

Molecularly target therapy; GIST shows a very dramatic response to tyrosine kinase inhibitor, imatinib. Imatinib was developed as a tyrosine kinase receptor inhibitor, which was shown to inhibit the intracellular kinases ABL and BCR-ABL fusion protein in chronic myeloid leukemia cells, but was subsequently found to have comparable activity against the KIT receptor and PDGFR. Imatinib has become a standard of care for advanced and metastatic disease (17,18).

Imatinib is a competitive antagonist of the adenosine triphosphate binding sites. Once absorbed, it binds to serum proteins (mainly albumin and alpha 1 acid glycoprotein) and peak concentrations are reached 4 hours after administration. Erythromycin, fluconazole and rifampicin have shown inhibition of imatinib metabolism. Alprazolam, caffeine, clindamycin, verapamil, clonazepam, and cortisol may cause toxic effects when given with imatinib.

Contrast enhanced CT and 18- FDG PET are routinely used in the assessment of imatinib response. The degree and pattern of enhancement observed on CT scans are useful for identifying post treatment changes (19). On CECT, a response to imatinib is characterized by rapid transition from a heterogeneously hyper-attenuating pattern to a homogenously hypo-attenuating pattern with resolution of the enhanced tumor nodules and a decrease in tumor vessels. This therapy decrease the density of tumor masses in GIST, so a disease that is initially judged as unresectable may become amenable to surgical excision after a major response induced by imatinib therapy and surgical resection is recommended for such patients because it is feared that residual GIST may develop secondary mutations that result in clinical resistance to imatinib and progression of disease (20). Optimal duration for imatinib therapy remains uncertain but most experts recommend life long therapy for advanced disease because studies have shown disease progression often follows shortly after the imatinib is stopped.

Side effects with imatinib therapy includes; (a) edema sopatients are advised to take low salt diet and diuretics. Tachyphylaxis is seen with side effect and it improves with continued therapy. (b) Nausea is usually mild and self limited and very less if the drug is given with food and in divided doses. (c) Muscle cramps are usually transient and self limited. (d) Cardiotoxicity: imatinib might damage cardiac myocytes.

Neoadjuvant and adjuvant imatinib; The success of imatinib in controlling locally advanced and metastatic GIST has led to interest in the neoadjuvant and adjuvant use of the drug. There have been studies suggesting a role for the neoadjuvant approach. Neoadjuvant is not recommended where a change in tumor size will not affect surgery. It can, however, be considered where a tumor response could permit function sparing surgery, e.g., rectum or esophagus.

The case resistant to imatinib or showing progression can be controlled by sunitinib. There has been growing interest in the use of VEGF inhibitors

such as Bevacizumab (A monoclonal antibody targeted against VEGF receptor).

Follow up; A high risk patient should have a CT scan every 3-4 months for 3 years, then every 6 months for 5 years. For low risk, a CT scan every 6 months for 5 years is acceptable (21).

In conclusion; gastrointestinal stromal tumors are soft tissue tumors that either express C-kit/CD 117 protein or have C-KIT or platelet-derived growth factor receptor-α mutations and show spindle cell or epitheloid morphology. Mutations cause constitutive activation of the KIT tyrosine kinase receptor, an important factor in the pathogenesis of this disease. Intestinal GISTs are more likely to be malignant than gastric GISTs. Complete excision is the initial treatment.The development of specific tyrosine kinase inhibitor, imatinib, has led to a breakthrough in the treatment of advanced disease. Patients with exon 11 mutations in the C-KIT gene are most likely to respond to this treatment than those with exon 9 or exon 13 mutations. There has been a drastic change in the surgical and oncological treatment approach to GIST patients.

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