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Gastrointestinal stromal tumors (GISTs): focus on histopathological diagnosis and biomolecular features

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Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract that are believed to originate from a neoplastic transformation of the intestinal pacemaker cells (interstitial cells of Cajal) normally found in the bowel wall or their precursors. Although the microscopic features have been known for a long time, the defining characteristic of GIST is the presence of the cell-surface antigen CD117 (KIT), which is demonstrated by immunohistochemistry. KIT, which is a growth factor transmembrane receptor, is the product of the proto-oncogene c-kit (chromosome 4). Surgical removal remains the only curative treatment for patients with GISTs. Tumor size, mitotic index, anatomic location, tumor rupture and disease-free interval are the classic characteristics used to predict the clinical course of patients who undergo complete gross resection.

Most GISTs express constitutively activated mutant isoforms of KIT or kinase platelet-derived growth factor receptor alpha (PDGFRA) that are potential therapeutic targets for imatinib mesylate. Imatinib mesylate is a rationally designed, molecularly specific oral anticancer agent that selectively inhibits several protein tyrosine kinases central to the pathogenesis of human cancer and which has demonstrated remarkable clinical efficacy in patients with chronic myeloid leukemia and malignant GISTs. More recently Sunitinib, a new KIT/PDGFRA kinase inhibitor, has been tested in patients with GIST resistant to imatinib, with promising results.

Key words: gastrointestinal stromal tumors, histopathological diagnosis, molecular biology, novel therapies

introduction

Gastrointestinal stromal tumors (GISTs) are specific mesenchymal tumors that may develop not only throughout the whole gastrointestinal (GI) tract but also in the omentum and mesentery. They range from small, benign, incidentally detected nodules to large malignant tumors. It has been suggested that GISTs originate from the interstitial cells of Cajal, which are intestinal pacemakers [1]. They derive from the myeloid stem cells, are positive for the CD34 antigen in 52%–72% of cases [2] and are frequently marked by the presence of the c-kit proto-oncogene (85%–94%). Cajal cells present both smooth muscle and neural cells, and neoplastic Cajal cells might preferentially express one, both or neither of these features, thus explaining the variant forms of GISTs. Although relatively rare, GISTs make up the largest subset of mesenchymal tumors of the GI tract and are reported to comprise ~5% of all sarcomas [3–5]. The estimated annual incidence is 10–20 cases per million, of which 20%–30% are malignant, although, following the recent clearer definition of the diagnostic criteria for GISTs, it may be necessary to revise these estimates [3].

GISTs occur in both sexes with similar frequency, but several reported data have shown a preponderance in males, generally after the fourth decade, with most studies finding a mean age at diagnosis of ~60 years. They are occasionally found in young adults, although extremely rare in children [4].

Such tumors may occur anywhere in the GI tract but are most commonly found in the stomach (4%–70%) and small intestine (20%–40%). Only 5%–15% are found in the colon and rectum, ~5% in the esophagus and in the omentum and rarely in the mesentery or retroperitoneum [5].

Surgical removal remains the only curative treatment for patients with GISTs. Tumor size, mitotic index, anatomic location, tumor rupture and disease-free interval are the classic features used to predict the clinical course of patients who undergo complete gross resection. Imatinib mesylate is a rationally designed, molecularly specific oral anticancer agent that selectively inhibits several protein tyrosine kinases central to the pathogenesis of human cancer which has demonstrated remarkable clinical efficacy in patients with chronic myeloid leukemia and malignant GISTs. More recently Sunitinib, a new KIT/PDGFRA kinase inhibitor, has been tested in patients with GIST resistant to imatinib, with

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promising results. The aim of this review is to clarify some aspect of histopathological diagnosis of GISTs and to review the most recent update in the medical management of GISTs [6, 7].

historical overview

Until 20 years ago, most mesenchymal tumors of the digestive tract were considered to be of smooth muscle or perineural origin. In 1983, Mazur and Clark [8] reported that many supposed smooth muscle tumors lacked immunohistochemical or electron microscopic evidence of smooth muscle or neural immunoreactivity, and they suggested that the neutral term 'gastric stromal tumor' would be more appropriate. Kindblom et al. [9] proposed that such tumors might originate from the interstitial cell of Cajal, an intestinal pacemaker cell, and suggested the name GI pacemaker cell tumor.

The term GIST was gradually adopted for a specific category of benign and malignant mesenchymal neoplasms of the GI tract with a minimal or incomplete myogenic or neural phenotype ('uncommitted phenotype') as defined by immunohistochemistry or electron microscopy. Tumors exhibiting true smooth muscle or Schwann cell (neural) differentiation are excluded. Although rare, GISTs are the most common mesenchymal tumors of the GI tract.

It has become clear that the tumor cells comprising GIST are closely related to the interstitial cells of Cajal [10, 11]. These cells constitute a complex cellular network, the likely functions of which are GI tract pacemaking and the regulation of intestinal motility. The immunohistochemistry of the interstitial cells of Cajal is similar to that of GIST cells, being positive for KIT [9, 12]. However, some GISTs arise from the mesentery or omentum, which lacks interstitial cells of Cajal, suggesting an origin in multipotential mesenchymal stem cells of Cajal cell lineage [13, 14].

pathology of GIST

Grossly, GISTs vary greatly in size, ranging from 1–2 cm to >20 cm in diameter. Upon gross examination, an untreated GIST is in most cases a friable mass that appears to arise in the muscle rather than in the epithelium of the GI tract; the tumors are often well circumscribed and unencapsulated, although a pseudocapsule may occasionally be seen. Large tumors may show cystic degeneration, necrosis and focal hemorrhage and may rupture at the time of surgical resection. Although extraluminal in origin, GISTs may ulcerate through the overlying mucosa [15].

Microscopically, 70% of GISTs appear as spindle cell tumors, 20% are epithelioid in appearance with the remainder having either a mixed spindle/epithelioid cell appearance or occasionally a carcinoid-like/paragangioma-like appearance [1]. The prognostic relevance of cell type seems limited, although in the past it was often suggested that the mitotic threshold for malignancy was lower in epithelioid tumors than in spindle cell tumors. GISTs of spindle cell type are composed typically of relatively uniform eosinophilic cells arranged in short fascicles or whorls. The tumor cells have paler eosinophilic cytoplasm than smooth muscle neoplasms, with syncytial appearance; nuclei tend to be uniform in appearance and more ovoid or shorter than those of a smooth muscle cytoplasm, often with vesicular chromatin. GISTs of epithelioid type are composed of rounded cells with variably eosinophilic or clear cytoplasm.

Epithelioid lesions, similar to spindle cell lesions, tend to have uniform round-to-ovoid nuclei with vesicular chromatin, and this subset of tumors shows a nested architecture more often than spindle cell cases, enhancing the risk of confusion with an epithelial or melanocytic neoplasm. Lesions of mixed cell type may exhibit an abrupt transition between spindle cell and epithelioid areas (necessitating careful sampling if both patterns are to be recognized) or may have a complex comingling of these cell types throughout, leading to an intermediate ovoid cytologic appearance.

immunophenotype

Although the microscopic features have been known for a long time, the defining characteristic of GIST is the presence of the cell-surface antigen CD117 (KIT), which is demonstrated by immunohistochemistry [16]. KIT, which is a growth factor transmembrane receptor, is the product of the proto-oncogene c-kit (chromosome 4). As a member of the tyrosine kinase receptor, KIT is closely related to the receptors for platelet-derived growth factor and other receptors of this family. KIT is expressed by hematopoietic progenitor cells, mast cells, germ cells and interstitial cells of Cajal. Activation of the KIT receptor by its ligand, known as stem-cell factor (SCF), leads to cascades involved in oncogenesis, including proliferation, adhesion, apoptosis and differentiation [16].

KIT positivity in GISTs is typically strong and global. Membrane staining is often present, and this pattern is more readily observed in epithelioid GISTs. Many GISTs also have paranuclear KIT-positive dots ('Golgi-zone pattern'), and spindle cell tumors usually have a pan-cytoplasmic appearing staining pattern, probably because membrane staining in these cells is difficult to observe due to the narrow cross-dimension of the spindle cells. Some epithelioid GISTs of the stomach are less uniformly positive (and sometimes only weakly positive) for KIT; the molecular correlation of this finding is under investigation.

The term 'GIST' should apply only to neoplasms displaying KIT immunopositivity with very rare exceptions. Such exceptions might include lesions with typical cytoarchitectural features of GIST but which appear to be immunohistochemically inert (e.g., due to some type of fixation artefact, excessive heat during section drying or very prolonged storage of unstained slides), are KIT negative due to sampling error (e.g., very small needle biopsies showing normal internal control staining for other antigens from tumors in which KIT staining is focal in distribution), have (in rare cases) ceased to express KIT due to some form of clonal evolution, perhaps following STI-571 therapy, or in the very small percentage (<2%) of otherwise typical tumors that lack either KIT mutations and/or KIT overexpression. Tumors in these exceptional categories should be labeled 'spindle cell (or epithelioid) stromal neoplasm most consistent with GIST' [5] and should be considered for molecular analysis for KIT or PDGFRA mutations. Immunohistochemistry should be performed without antigen retrieval since this may yield false-positive CD117 staining; similarly, Bouin fixation should be avoided since it may impair the feasibility of molecular analysis on fixed samples.

Approximately 70%–80% of GISTs are also positive for CD34, a hematopoietic progenitor cell antigen also present in endothelial cells and subsets of fibroblasts and many neoplasms related to these cell types. GISTs of the esophagus and rectum are more consistently CD34 positive than are the gastric and small intestinal GISTs. Approximately 30% of GISTs, especially gastric and small intestinal tumors, are positive for smooth muscle actin (SMA), whose expression tends to be reciprocal with that of CD34; sometimes this is seen in one tumor where CD34-positive and actin-negative areas and CD34-negative and actin-positive areas are present. S100 protein expression is relatively rare in GISTs and occurs most commonly in the small intestine (10%). The positivity is usually focal, but is present in both cytoplasm and nuclei, and most likely represents true expression of this antigen. Positivity for desmin, the muscle-type intermediate filament protein, is rare in GISTs at all sites but has been observed relatively more often among esophageal GISTs [17]. Like most mesenchymal tumors, especially those that are malignant, GISTs are positive for vimentin. Keratin positivity is rare (approximately 10% of cases) and can be seen with antibodies reacting to keratin 18 and, to a lesser degree, to keratin 8 [18].

Attempts to correlate cellular morphology with immunophenotype have not been successful. Two-thirds of spindle cell tumors express desmin and muscle actin but usually in <10% of the tumor cells. Only 20% express desmin and 40% express SMA in a diffuse manner. Of the round cell tumors, <10% express desmin and SMA. Myxoid tumors, with demonstrated smooth muscle differentiation, can be confused with mucin-producing adenocarcinoma or neoplasms with clear cell or signet-ring cell features. Furthermore, cellular morphology can be misleading, since tumors undistinguishable from schwannoma have revealed strong desmin expression. However, schwannomas are negative for CD117 and CD34 and positive for S-100 [19].

molecular analysis of GISTs

Most GISTs express constitutively activated mutant isoforms of KIT or kinase PDGFRA.

KIT is an oncogenic receptor tyrosine kinase (RTK) activated by binding with its ligand SCF. The KIT activation results in phosphorylation of various substrates that mediate intracellular signal transduction. KIT receptor is composed by an extracellular region of five immunoglobulin-like loops, followed by a transmembrane domain, an intracellular domain which contains a negative regulatory juxtamembrane domain and a tyrosine kinase which presents regions: the ATP-binding pocket and the phosphotransferase catalytic site. Similar to KIT, PDGFRA is also a RTK with similar structure, and in GIST, the KIT or PDGFRA mutations cause phosphorylation, constitutive activation of these kinase receptors and its downstream signal. These receptors are potential therapeutic targets for imatinib mesylate [20], which is a c-kit/PDGFR tyrosine kinase inhibitor, acting on c-kit and PDGFR activity by binding to the ATP site and preventing the activation of PI-3K.

More than 90% of GIST present KIT mutations occurring mainly in exon 11 (50%–77%), exon 9 (10%–18%), exon 13 (1%–4%) and exon 17 (1%–4%).

The exon 11 mutation frequency among low-risk patients was of 87%, while exon 9 mutations were more frequent in frankly malignant GIST (17%) than low- or high-risk tumors (3% each).

On the other hand, patients whose tumors contained exon 11 KIT mutations had a longer event-free and overall survival than those whose tumors expressed either exon 9 KIT mutations or had no detectable kinase mutation. Exon 11 mutations had a higher response to imatinib and longer time to progression than those with exon 9 mutations. Regarding PDGFRA mutations, these occur mainly in exon 18 (4%–7%), exon 12 (2%–6%) and exon 14 (<1%) [21].

In conclusion, mutations of KIT or PDGFRA are found in the vast majority of GISTs, and the mutational status of these oncoproteins is predictive of clinical response to imatinib. PDGFRA mutations may explain response and sensitivity to imatinib in some GISTs-lacking KIT mutations.

prognosis

GISTs are generally thought to be malignant, but they have different degrees of aggressiveness, which result in different times for the development of metastases. Predicting the potential biological behavior of these tumors remains difficult and an analysis of the literature to resolve this issue provides many conflicting reports. Tumor size, mitotic activity, tumor necrosis, histological type and pattern, immunohistochemical profile, staining for proliferating antigens and ploidy status, among others, have all been evaluated extensively in this context without any consensus being established.

The most important and easily applicable morphologic criteria for prediction of tumor behavior are tumor size (maximum diameter in centimeters) and mitotic rate. These criteria should be applied together, and they form the current basis of prognostic evaluation by pathologists. However, the significance of size is site dependent; specifically, gastric tumors tend to be less aggressive than intestinal tumors, even those >5 cm in size, provided that their mitotic activity is low, no more than five of 50 high-power fields (HPFs). Most GISTs of <2 cm have negligible mitotic activity (usually less than five of 50 HPFs). Such tumors are largely benign in all sites when completely removed.

A consensus statement [6] has suggested that patients with GISTs may be categorized into very low, low, intermediate and high-risk tumors on the basis of an estimation of their potential for recurrence and metastasis. Very low-risk tumors are defined as tumors of <2 cm with fewer than five mitoses per 50 HPFs. Low-risk tumors are defined as tumors of between 2 and 5 cm with fewer than five mitoses per 50 HPF. Intermediate risk tumors are defined as tumors of <5 cm with six to 10 mitoses per 50 HPF or tumors of between 5 and 10 cm with fewer than five mitoses per 50 HPF. High-risk tumors are defined as tumors >5 cm with more than five mitoses per 50 HPF, tumors >10 cm with any mitotic rate or any size tumors with >10 mitoses per 50 HPF [2, 6]. Nevertheless, the subjectiveness and lack of concordance between observers during mitotic counting are important limitations to this method; factors such as size and number of fields examined, tissue section thickness, variation in tumor cellularity and in tumor cell size, morphological criteria for the identification of mitotic figures and fastidiousness of the observer, bias the results and reduce the reproducibility of this criterion [2, 6].

molecular pattern of resistance to imatinib

The KIT or PDGFRA RTKs are constitutively activated by gain-of-function mutations in most GISTs, and these mutations are early events in GIST oncogenesis.

Clinical responses to imatinib depend on the exonic location of KIT mutations in GIST, and 10%–20% of GIST patients exhibit primary resistance to imatinib.

Primary resistance is generally defined as progression within the first 6 months of imatinib treatment. This progression is generally multifocal and this subgroup of GISTs usually expresses wild-type KIT or mutations in exon 9 of KIT or mutated PDGFRA with a D842V mutation.

Secondary resistance is therefore defined as resistance occurring beyond this 6-month period and is the result of selection for additional point mutation in the KIT kinase domains. On the other hand, there are also nonidentified mutations in the nonresistant GIST.

Two mechanisms explain how those secondary mutations can induce resistance to imatinib: first, the mutation can stabilize the active conformation of the KIT kinase preventing the imatinib binding, and second, the mutation may interfere with imatinib binding without affecting kinase conformation.

Usually, most resistant tumors with a secondary mutation had primary mutations in exon 11. The second site mutations are mainly substitutions involving exon 13, 14 and 17 KIT corresponding to the kinase domain [22–24]. Recent study suggests that primary kit mutations in exon 13 K642E [5] and in exon 14 T670I were associated with acquired resistance [25].

All these mutations alter the secondary structure of the kinase domain with the resulting alteration of the interaction between imatinib and the receptor.

A frequent secondary mutation involves the exon 13 codon 654 (V654A) which decreases the binding affinity between imatinib and the receptor and increases the sensitivity to low concentrations of SCF [26].

A second mutation that may confer imatinib resistance is located in exon 11 cod816 (D816V), since this activates the kinase domain conformation, and the receptor is unable to bind the imatinib [26]. Cells with these mutations showed more sensitivity to nilotinib, a phenylaminopyrimidine related to imatinib but in any case was insufficient as an adequate treatment choice.

A third mutation involved in KIT secondary mutation is in exon 17; these are essentially substitutions involving N822K, D820Y and Y823D [24–27]. In untreated GIST, the incidence if exon 13, 14 and 17 mutations is ∼1%.

Moreover, secondary resistance occurs according to two different patterns of partial and multifocal resistance. In the first subgroup, in which one or a limited number of metastases show an enlargement but the other sites remain controlled by imatinib, a multidisciplinary approach is considered, and possible strategies include the combination of locoregional approaches and either an increased dosage of imatinib or an alternative experimental targeted therapy. On the other hand, in the second subgroup, increasing the dose of imatinib or an alternative targeted therapy are both potentially suitable strategies, while surgery or radiofrequency ablation are less useful.

The multitargeted KIT inhibitor sunitinib has proven effective in some patients with imatinib-resistant GIST and has achieved regulatory approval for this clinical indication, whereas other novel inhibitors of KIT, such as PKC412, show promising preclinical activity against certain imatinib-resistant mutations in GISTs.

sunitinib

Sunitinib is an orally administered small molecule that inhibits multiple RTKs. Sutent (Pfizer, Inc., New York, NY) is the malate salt of sunitinib. Targets of sunitinib include vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), platelet-derived growth factor receptors (PDGFRA and PDGFR beta), SCF receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor type 1 (CSF-1R) and the glial cell line-derived neurotrophic factor receptor (RET). The ability of sunitib to target multiple tyrosine kinases in addition to kit has suggested that it might be active in imatinib-resistant tumors [28].

The study [29] supporting the approval of sunitinib for second-line treatment of GIST is a randomized, double-blind clinical trial performed in 56 centers in Asia, Europe and North America, including 22 centers in the United States. Eligible patients were adults with radiographically measurable GISTs following either documented progression on or intolerance to imatinib. Treatment was administered in repeated 6-week cycles. Patients received either oral sunitinib malate (50 mg) or placebo daily for 4 weeks followed by 2 weeks of rest (schedule 4/2). Following Response Evaluation Criteria in Solid Tumors-defined disease progression, patients on the placebo arm who met crossover eligibility criteria were offered the opportunity to receive open-label sunitinib.

The primary end point was time-to-tumor progression (TTP). Secondary end points included overall survival, progression-free survival (PFS) and confirmed objective response rate.

Three hundred and twelve patients randomly assigned 2:1 to sunitinib versus placebo comprised the intention-to-treat population. After 149 progression events had occurred, the first interim analysis for efficacy revealed that patients receiving sunitinib experienced a more than four-fold increase in median TTP from 6.4 to 27.3 weeks (hazard ratio, 0.33; 95% confidence interval, 0.23, 0.47; log-rank $P < 0.0001$). Further data are warranted to confirm this preliminary observations.

conclusion

GISTs are relatively rare neoplasms of the GI tract that may have a potentially lethal clinical outcome. Classification of GISTs by pathologist has been controversial because the histologic appearance of GIST is often consistent with other tumors such as leiomyomas and leiomyosarcomas.

Molecular-targeted therapy can be effective in the advanced disease setting, resulting in major tumor responses. Antitumor activity may be highly predictable by assessing tumor molecular biology.

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