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Current Concepts on GIST
Imatinib: One Size does not Fit All!

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Stromal or mesenchymal neoplasms affecting the gastrointestinal (GI) tract typically present as subepithelial neoplasms, and they are divided broadly into two groups. The most common group consists of neoplasms that are collectively referred to as gastrointestinal stromal tumors (GISTs). They are most often located in the stomach and proximal small intestine, but can occur in any portion of the alimentary tract including occasionally in the omentum, mesentery, and peritoneum [1-5]. The current view is that the overwhelming majority of mesenchymal tumors arising in the GI tract fall into the GIST category, and they are identified mainly by expression of KIT protein; as a group, these tumors are more specifically defined by the presence of activating mutations in the KIT or platelet-derived growth factor receptor A (PDGFRA) genes.

A far less common group of mesenchymal GI tract neoplasms is comprised of a spectrum of tumors that are identical to those that might arise in the soft tissues throughout the rest of the body. These include lipomas, liposarcomas, leiomyomas, true leiomyosarcomas, desmoid tumors, schwannomas, and peripheral nerve sheath tumors [6].

GISTs that arise in adults are characterised by the near-universal expression of the CD117 antigen, in contrast to other spindle-cell tumors of the GI tract (ie, leiomyomas, leiomyosarcomas), which are typically CD117-negative. The CD117 antigen is part of the KIT transmembrane receptor tyrosine kinase that is the product of the KIT (also denoted c-kit) protooncogene. In more than 80 percent of GIST cases, a mutation in the KIT gene leads to an abnormally activated KIT protein and enables oncogenic signaling in the cell [7-9]

A subset of GISTs lacking KIT mutations have activating mutations in the gene that encodes a related receptor tyrosine kinase, platelet-derived growth factor receptor alpha (PDGFRA) [10-12].

Approximately 5 percent of GISTs do not have a detectable KIT or PDGFRA mutation. These so-called wild-type tumors are a heterogeneous group, some of which are driven by oncogenic mutations acting downstream from the receptor kinases. Wild-type GISTs have one of several familial autosomal dominant syndromes as those that arise in neurofibromatosis-1 (NF1 gene mutation), the Carney-Stratakis syndrome (SDHX subunit mutations), and Carney triad (possibly related to epigenetic changes in the SDHC promoter that silence gene expression), [13,14].

These families have a predisposition to multiple gastric and small bowel GISTs, and in some cases, skin hyperpigmentation, dysphagia, or GI autonomic nerve tumors such as paragangliomas.

Many of these have mutations in the SDHX gene that encodes a subunit of the SDH enzyme or an epigenetic methylation of the SDH subunit C (SDHC) gene promoter, which leads to silencing of SDHC gene expression [15].

The clinical behavior of GISTs is highly variable; the main prognostic determinants are tumor size, mitotic rate, and tumor location and that led to the foundation for the NIH 2002 consensus approach to GIST risk stratification. One of the tenets of this risk stratification schema is that virtually all GISTs (especially those larger than 1 cm) have malignant potential, a concept supported by three large retrospective studies from the Armed Forces Institute of Pathology (AFIP), [2,16,17].

Taken together, these studies indicate that all GISTs larger than 2 cm have some finite risk of recurrence, while gastric GISTs that are 2 cm or less in size with a low mitotic rate can be regarded as having an exceedingly low recurrence risk. However, until long-term data on the natural history of GISTs <2 cm in size from all sites are known, it is misleading to regard any as being truly "benign.

The management of GISTs involving the gastrointestinal (GI) tract depends upon the confidence in the preoperative diagnosis, tumor location and size, extent of spread, and clinical presentation (eg, whether there is evidence of tumor obstruction, perforation, or uncontrolled hemorrhage).

Some general surgical principles apply to these tumors regardless of location:

- Preoperative biopsy or endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy (FNA) may not be necessary if a mesenchymal GI tumor is strongly suspected, it appears to be resectable, and the patient is otherwise operable. However, a biopsy is preferred to confirm the diagnosis if metastatic disease is suspected or if preoperative imatinib is considered prior to attempted

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resection in a patient who has a large locally advanced lesion thought to represent a GIST.

- All GISTs ≥2 cm in size should be resected. However, there is no consensus on the management of smaller GISTs The natural history of these and other GISTs between 1 and 2 cm, including their growth rate and metastatic potential, remains unknown. Although these small GISTs may be followed endoscopically until they grow or become symptomatic, the optimal frequency of follow-up and specific risks of this strategy is uncertain [18].

Surgical resection is the treatment of choice for potentially resectable tumors; however, initial therapy with imatinib may be preferred if a tumor is borderline resectable, or if resection would necessitate extensive organ disruption.

The goal of surgical treatment is complete gross resection with an intact pseudocapsule, if possible. Segmental resection of the stomach or intestine should be performed with the goal of achieving negative resection margins. Wider resection of uninvolved tissue is of no additional benefit. Routine lymphadenectomy is unnecessary because nodal metastases are rare [19].

The necessity of achieving negative microscopic margins is uncertain with large (>10 cm) GISTs. The management of a positive margin according to the final pathology report is not well defined and depends on whether the surgeon believes the finding accurately reflects the surgical procedure that was undertaken [20].

Although patients who undergo a microscopically incomplete resection may be at greater risk for a locoregional recurrence, other factors such as tumor grade and size may play a more significant role in determining the risk of recurrence. The risks and benefits of reexcision versus initiation of imatinib must be carefully considered [21].

Before 2001, surgery was the only available treatment for GISTs. In approximately one-half of patients, complete resection was not possible, and median survival ranged from 10 to 23 months [22]. Dramatic improvements occurred with the recognition that mutational activation of the KIT or PDGFRA genes stimulated the growth of these cancer cells. This led to the development of effective systemic therapies in the form of small molecule tyrosine kinase inhibitors (TKIs) such as imatinib. Following the introduction of imatinib, the median survival of advanced GIST extended to 60 months in the trial with the longest follow-up to date [23].

The success of these agents in the setting of advanced disease prompted interest in their use as adjuvant treatment for patients at high risk of recurrence after complete resection.

For patients who undergo initial resection, rather than neoadjuvant imatinib, the decision to pursue adjuvant imatinib depends on an estimation of the risk of recurrence, which is typically based upon tumor size, mitotic index, location within the GI tract, and the presence or absence of tumor rupture (either spontaneously or during surgery). Regardless of the tool used for risk stratification, we reserve adjuvant imatinib for those patients who meet criteria for "high-risk" and who have an estimated risk of recurrence that is >30 to 50 percent.

Molecular analysis on all tumors should be performed if adjuvant imatinib is being considered. For patients with a PDGFRA D842V mutation, or an SDH-deficient or NF-related GIST, adjuvant imatinib has no benefit. For other patients, the usual dose of imatinib for adjuvant therapy is 400 mg daily. Based upon an analysis of data from the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial, for patients who harbor an exon 9 KIT mutation, which confers relative resistance to adjuvant imatinib, a dose of 800 mg per day may be preferred, if tolerated [24]. Based upon the results of the Scandinavian Sarcoma Group (SSG) XVIII adjuvant trial, imatinib treatment for 36 months or longer is preferred over shorter durations of treatment [25].

However, a number of clinical questions remain, including long-term benefit of such therapy, optimal disease risk stratification, and the optimal duration of adjuvant treatment.

Given the high response rates to imatinib (and the potential for complete pathologic response in the setting of advanced disease), there are several clinical scenarios in which preoperative (neoadjuvant) imatinib could be considered. This includes an unresectable or borderline resectable primary tumor, a potentially resectable tumor that requires extensive organ disruption, a local recurrence of locally advanced disease, or a limited amount of potentially resectable metastatic disease. In all cases, the goal of treatment is a reduction in tumor size that may facilitate complete surgical resection and/or increase the likelihood of organ preservation.

There is no consensus among expert groups as to the indications for neoadjuvant therapy. Some limit this approach to patients with identifiable high-risk characteristics (size >5 cm, >5 mitoses/50 HPF, anatomic location resulting in a potentially morbid resection). Consensus-based guidelines from the NCCN recommend initial treatment with imatinib for patients with marginally resectable tumors and for those who have potentially resectable disease but with the risk of significant morbidity. Examples might include a GIST arising in the esophagus, esophagogastric junction, duodenum, or distal rectum. At these sites, preoperative treatment might shrink the tumor and permit a more conservative local excision to be performed, rather than radical surgery [26-28].

The advent of imatinib mesylate has revolutionised the treatment of patients with unresectable or metastatic GIST and new therapeutic approaches have emerged regarding resectable and marginal resectable disease.Current evidence from recent studies provide a strong rationale for continuous imatinib treatment for 3 years following surgical resection and long-term continuous administration in advanced or metastatic GIST

In conclusion, the two cases with GIST in Kalliakmanis et al paper published in this issue, represent the two aspects of the same coin. The same disease but different natural history, and the key to predict the disease's behaviour in our days is by molecular analysis (gene mutation).

Based on these information it seems that imatinib is not the magic bullet any more and this explains the recurrence seen years later in one of the cases.

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