Arabic summary

Recent Advances in Management of Gastrointestinal Stromal Tumours

Essay

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List of Abbreviations

ALK	Anaplastic Lymphoma Kinase
BID	Twice daily
CB	Clinical benefit
CML	Chronic myeloid leukemia
CR	Complete response
CT	Computed Tomography
DFS	Disease free survival
DOG1	Discovered on GIST
EGIST	Extra gastrointestinal stromal tumours
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasonography
FNA	Fine needle aspiration
FDA	Food and drug administration
FDG	Fluoro-2-deoxy-D-glucose
GI	Gastrointestinal
GISTs	Gastrointestinal stromal tumors
HAE	Hepatic artery embolization
HACE	Hepatic arterial chemoembolization
HPF	High power field

ICCs	Interstitial cells of Cajal
IHC	Immunohistochemical
LMP	Low malignant potential
MRI	Magnetic Resonance Imaging
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
OD	Once daily
OS	Overall survival
PAS	periodic acid Schiff
PD	Progressive disease
PDFGRA	Platelet-derived growth factor receptor alpha
PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Partial response
RFA	Radiofrequency Ablation
RFS	Recurrence-free survival
SCF	Stem cell factor
SD	Stable disease
SMA	Smooth muscle actin
SMTs	Submucosal tumours
TKI	tyrosine kinase inhibitor
TTP	time to disease progression
UGI	Upper gastrointestinal
VEGFR	Vascular endothelial growth factor receptor

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Neoplastic GIST cells seem to arise from a common precursor cell, which gives rise to the interstitial cells of Cajal in the normal myenteric plexus. **(Demetri et al., 2010).**

The incidence of GISTs is estimated to be approximately 10-20 per million people, per year. Malignancy possibility is 20-30%. However, the precise incidence of GISTs is unknown because of the incomplete definition and classification. Over 90% of GISTs occur in adults over 40 years old, with a median age of 63 years. However, GIST cases have been reported in all ages, including children. The incidence between the sexes is the same, although a study reported that there is a slight predominance of males. There are no elements that indicate any association with geographic location, ethnicity, race or occupation. **(Tran et al., 2005).**

The most common site of primary tumors is the stomach (39% to 70%); followed by the small intestine (31% to 45%); colon, rectum, and anus (10% to 16%); and mesentery and peritoneum (8%); with rare cases arising in the esophagus. **(Miettinen et al., 2000).** Metastatic disease is most often found in the liver, peritoneum, and omentum**. (Lasota, 2001).** Less

common metastatic sites include lung and bone. **(Hughes et al., 2004)**.

GISTs most commonly results from activating mutations in one of the receptor protein tyrosine kinases: KIT (CD117) or platelet-derived growth factor receptor alpha (PDGFRA). **(Demetri et al., 2010).**

GISTs have specific immunohistochemical (IHC) markers: 95% are CD-117 positive, 70-80% are CD34 positive, and 20-30% are smooth muscle actin (SMA) positive, whereas desmin is positive in less than 5% of GISTs. Discovered on GIST (DOG) 1, known also as ANO1, has emerged in recent years as a promising biomarker for GISTs, since recent studies documented that DOG1 antibodies are more sensitive than kit antibodies in detecting gastric GISTs and tumours carrying PDGFR alpha mutations. **(Caterino et al., 2011).**

GISTs have an uncertain clinical behavior ranging from benign to frankly malignant, making the outcome totally unpredictable. Multiple parameters have been considered as predictors of malignancy. Size and mitotic count appear to be the most useful predictors of the malignant behaviour. **(Gupta et al., 2008)**.

The clinical presentation of patients with GISTs varies depending on the anatomic location of the tumor and the tumor size and aggressiveness. **(Demetri, 2008).** Approximately 70% of GISTs are symptomatic, 20% are asymptomatic and identified during staging or follow-up for other malignancies, while 10% are discovered during autopsy. **(Gold & DeMatteo, 2006).**

GISTs vary greatly in size from a few millimeters to >30 cm, the median size though is between 5 cm and 8 cm. Macroscopically, GIST usually has an exophytic growth and as a result, the intra-operative appearance commonly resembles of a mass, that is attached to the stomach, projecting into the abdominal cavity and displacing all the other organs**.** **(Stamatakos et al, 2009).** Small GISTs may form solid subserosal, intramural, or, less frequently, polypoid intraluminal masses. Large tumors tend to form external masses attached to the outer aspect of the gut involving the muscular layers. GISTs morphology is quite varied; the tumors are composed of the following: Spindle cells (70%), Epithelioid cells (20%), Mixed spindle and epithelioid cells (10%). **(Corless & Heinrich, 2008).**

GISTs encompass a broad continuum of histologic patterns, ranging from bland-appearing tumors with very low mitotic activity (often previously designated leiomyomas) to very

aggressive-appearing patterns (previously often called leiomyosarcomas). **(Edge et al., 2010).**

Treatment may involve surgery and/or the use of tyrosine kinase inhibitors (TKI) depending on the extent of disease and tumor sensitivity to TKIs. **(Judson & Demetri, 2007).**

The standard of care in the management of patients with GISTs had rapidly changed after the introduction of TKIs, such as imatinib mesylate and sunitinib malate. **(Demetri et al., 2010).** Most GISTs have mutations in the KIT or PDGFRA gene, causing activation of tyrosine kinase. Imatinib (a TKI) is the first-line palliative treatment for advanced GISTs. Sunitinib was introduced for patients with mutations not responsive to imatinib**. (Sjölund et al., 2010).**

Despite the proven success of imatinib and other newer tyrosine-kinase inhibitors, surgical resection remains the treatment of choice and offers the only chance for cure from GIST. The aim of surgical treatment is complete resection, avoiding tumour rupture, preferring wedge resections whenever possible; lymphadenectomy is not recommended due to the rarity of nodal metastasis, with the exception of GISTs occurring in a setting of Carney triad, that usually show an higher rate of lymph nodes metastasis. **(Zhang et al., 2010).**

The main operative principle is resection of the tumor with negative microscopic margins. Wide resection of the tumor (e.g., 2 cm margin) has not been shown to improve outcomes and expert consensus is that such dogmatic adherence to a particular width of margin is not necessary or recommended. **(Bucher et al., 2006).**

Because adequate resection for small malignant GISTs can be achieved by wedge resection, minimally invasive surgery techniques can be considered in selected cases. In recent years, numerous published reports of laparoscopic resection of gastric GISTs have demonstrated the feasibility and safety of this technique. **(Bedard et al., 2006).**

Clinical picture

1-Predisposing factors:

In rare cases, GISTs have been found in several members within the same family. These family members inherited a gene mutation that leads to GIST. But most GISTs are sporadic and their cause is unknown **(Corless et al., 2004)**.

Familial gastrointestinal stromal tumor syndrome is a rare, inherited condition leading to increased risk of developing one or more GISTs. The mutated gene passed from one generation to the next in the familial GISTs syndrome is usually the c-kit gene. This is the same gene that is mutated in sporadic GISTs. But patients with the familial form have a mutation in all the cells of their body, whereas only the GIST cells are affected by this mutation in the sporadic form. Very rarely, another gene, the Platelet derived growth factor alpha (PDGFRA) gene (instead of the c-kit gene) is responsible for GISTs in some families. Patients with this inherited condition tend to develop GISTs at a younger age than do sporadic GIST patients and are more likely to have multiple GISTs. They may also have skin spots similar to those in neurofibromatosis. Until recently, when tests for c-kit gene and PDGFRA gene became available, some of these patients

were mistakenly thought to have neurofibromatosis **(Raut et al., 2007)**.

Carney triad, familial gastrointestinal stromal tumor syndrome, and von Recklinghausen syndrome are associated with an elevated risk of developing GISTs. Specific associations of GISTs with other malignancies have not been determined, but GISTs are not infrequently seen with other neoplasms. No risk factors or causative factors have been identified **(Dirnhofera & Leyvrazb, 2009).**

GISTs have rarely been reported in patients with AIDS. The few sporadic cases are from pediatric and adult patients with AIDS who were diagnosed with malignant GISTs **(Padula et al., 2005)**.

2-Pathophysiology:

A-Epidemiology:

Although gastrointestinal stromal tumors are generally regarded as a rare tumor, it is the most common (80%) mesenchymal neoplasm of the GI tract and represents about 5% of all sarcomas **(Bayraktar et al., 2010)**.

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30%. However, the precise incidence of GIST is unknown because of the incomplete definition and classification.

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GISTs tumors may occur anywhere along the length of the digestive tract from the esophagus to the anus. They account for 1–3% of gastric neoplasms, 20% of small bowel tumors and 0.2–1% of colorectal tumors **(Nikolaos et al., 2005).**

The most common location of GIST is stomach (50-60%) and small intestine (30%-40%). Five to ten percent of GISTs arise from the colon and rectum, and 5% are located in the esophagus. Other less common locations are those outside of the GI tract, like mesentery, retroperitoneum and omentum. However, there have been reported rare cases in the gallbladder, pancreas, liver and urinary bladder. In cases, where GIST occurs outside the GI tract, the tumors are known as extra - gastrointestinal stromal tumors (EGISTs**) (Stamatakos et al., 2009)**.