Recent Modalities in Management of Gastrointestinal Stromal Tumors

Essay

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وعلَّمَكَ مَا لَمْ تَكُنْ
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List of Abbreviations

AFIP	: Armed forces institute of pathology
ATP	:adenosine triphosphate
CD	:Cluster of differentiation
CECT	:contrast enhanced computed tomography
CR	: Complete response
DFS	:Disease free survival
DSS	:disease-specific survival
EGISTs	:Extra gastrointestinal stromal tumors
EUS	:Endoscopic ultrasonography
ESMO	:European society of medical oncology
FDG	:fluoro-2-deoxy-D-glucose
FNA	:fine needle aspiration
GI	:Gastrointestinal
GISTS	:Gastrointestinal stromal tumors
GIST/Ls	:Gastrointestinal stromal tumors and leiomyoma's
GIT	:Gastrointestinal tract
HAE	:Hepatic arterial embolization
HPF	:High power field
ICCs	:Interstitial cells of Cajal
IHC	:Immunohistochemistry
IM	:Imatinib Mesylate
LMP	:Low malignant potential
MRI	:Magnetic resonanc image
NCCN	:National Comprehensive Cancer Network
NF1	:Neurofibromatosis type one
OS	:Overall survival
PDGFRα	:Platelet-derived growth factor receptor alpha
PET	:Positron Emission Tomography
PFS	:Progression-free survival
RFS	:recurrence-free survival
RR	:Response rate
SDH	:succinate dehydrogenase
SMA	:Smooth muscle actin
VCE	:Video capsule endoscope

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract ***(Demetri et al., 2007).***

GISTs are rare, accounting for only 1% to 3% of all malignant gastrointestinal tumors and only ***(Lamba et al.,2012).*** The annual incidence of GIST is 11 - 14/million annually and the median age of diagnosis is 60 years (range 51 - 60***)(Rammohan et al., 2013)***.

These tumors are very rare in the pediatric population, with <1% occurring prior to age 21***(Miettinen and Lasota, 2013).***

Mesenchymal tumors are a family of related tumors including those named plexosarcomas, leiomyoblastomas, leiomyosarcomas, GISTs, gastrointestinal autonomic tumors (GANTs), and gastrointestinal pacemaker cell tumors (GIPACTs) ***(Megan et al., 2004).***

The first accurate description of mesenchymal neoplasms of the gastrointestinal tract (GIT) was in 1941. Traditionally, these tumors were thought to be derived from smooth muscle cells, based on their resemblance to smooth muscle tumors and they were designated as leiomyomas, bizarre leiomyomas, cellular leiomyomas and leiomyosarcomas. However, with the advent of electron

microscopy, it has been shown that relatively few neoplasms showed convincing ultrastructural evidence of smooth muscle differentiation. The application of immunohistochemistry revealed that many of these neoplasms lacked the immunophenotypical features of smooth muscle differentiation ***(Muna et al., 2005).***

The term Gastrointestinal stromal tumors (GISTs) was first used, and includes a heterogeneous group of non epithelial neoplasms with spindle or epithelioid cells, which may display myogenic features (smooth muscle GISTs), neural attributes (gastrointestinal autonomic nerve tumor), or characteristics of both muscle and nerve (mixed GISTs), or may lack differentiation (GISTs not otherwise specified) ***(Nikolaos et al., 2005).***

Subsequently, the concept of 'plexosarcoma' with the existence of a small subset of stromal tumors with autonomic neuronal differentiation, became better known as gastrointestinal autonomic nerve tumors (GANTs**)** ***(Muna et al., 2005).***

With the advent of immunohistochemical analysis a definition of a new entity among the gastrointestinal mesenchymal tumors called the gastrointestinal stromal tumors (GISTs) which particularly express the c-kit (CD117) protein a growth factor trans-membrane receptor with tyrosine kinase activity ***(Daniel et al., 2005).***

They may occur anywhere along the length of the digestive tract from the esophagus to the anus. They account for approximately 1-3% of gastric neoplasms, 2% of small bowel tumors and 0.2-1% of colorectal tumors. Approximately 60-70% of the GISTs arises in the stomach, 20-30% in the small intestine, 5% in the colon and rectum, less than 5% in the esophagus and sometimes develops outside the intestinal tract, in the abdominal cavity ***(Nikolaos et al., 2005).***

There was considerable controversy as to the line of differentiation, since some tumors exhibited a myogenic phenotype, others showed neural differentiation, some revealed mixed differentiation and some cases did not show any specific line of differentiation, the 'null phenotype' ***(Muna et al., 2005).***

GISTs were divided into four major types: smooth muscle; neural; combined smooth muscle-neural; and uncommitted. Recent studies have reported GIST cells demonstrating characteristics similar to those of the interstitial cells of Cajal (ICC), or 'pacemaker cells', which play a neuromotor role in normal gut motility ***(Ken-ichi et al, 2006).***

GISTs also vary greatly in size, morphology, and malignancy potential, creating a continuum of neoplasms with uncertain malignancy potential ranging from virtually

benign tumors to overtly malignant, aggressive cancers. The more indolent GISTs are typically small, whereas other GISTs may present with overt metastases already at the time of the diagnosis ***(Heikki,2006).***

GISTs typically arise in the bowel wall, usually from the muscularis propria, and may extend intra- or extraluminally ***(Sullivan et al., 2006).***

GISTs arise from activating mutations in KIT or platelet-derived growth factor receptors α (PDGFRα) ***(Michael,2006).*** In the 1990s, investigators noted similarities between GIST cells and the interstitial cells of Cajal, a group of cells located in the muscularis propria and around the myenteric plexus throughout the GI tract,serving as pacemakers for peristaltic contraction ***(Janeway et al., 2007).***

Immunohistochemically, the tumor cells revealed a phenotype similar to Cajal cells, occasionally with differentiation to smooth muscle cells or neural cells. Non-epithelial tumors originating from the gallbladder are rare. Among these, rhabdomyosarcoma, malignant fibrous histiocytoma, and angiosarcoma reportedly represent malignant mesenchymal tumors **(*Makoto et al., 2005).***

Risk factors and aetiology are unknown, but there is a rare association with neurofibromatosis type. Some studies show no significant sex difference, whilst others show a male predominance.. Sporadic instances are rare before the age of

forty. However, GISTs can be familial, thus can be present in younger patients ***(Sullivan et al., 2006).***

Primary GISTs may occur in locations other than gastrointestinal tract for example the first case of a large Primary gastrointestinal stromal tumor presenting as a uterine mass in a 77-year-old female. It is extremely rare that these tumors occur in the bile tract ***(Makoto et al., 2005).***

It is generally accepted that the criteria needed for predicting biological behavior may differ significantly with location. For example, in the colon, size smaller than 2 cm and mitotic rate less than 1 mitosis /50 High power field (HPF) are indicators of benignity, while size larger than 5 cm and mitotic rate greater than 5/10 are generally accepted as predictors of malignancy **(*Hillemanns et al., 2005).***

This lack of clarity in distinguishing GISTs can potentially affect clinical decision-making, because non-GISTs included in the differential diagnosis are sensitive to systemic chemotherapeutic treatment, whereas GISTs are resistant. Surgical resection was historically the only therapy with efficacy in true GISTs. However, even complete surgical resection of primary GIST carried a substantial risk for recurrence ***(Charles, 2006).***

The clinical presentation of GIST is erratic. Furthermore, only 70% of the patients are symptomatic, while 20% are asymptomatic and 10% are detected at

autopsy.***(Kim et al., 2005)***.

GISTs evaluation can be done with many imaging methods like: ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission transverse tomography (PETT). CT-scan can detect small intestinal tumors and guide the biopsy, it is an accessible and sensitive method especially in case of liver metastasis and also provides useful information about the response to the treatment and about the recurrence ***(Rosenbaum et al., 2006).***

Surgery is the mainstay of therapy for non metastatic GISTs. Lymph node metastasis is rare and routine removal of lymph nodes is typically not necessary, also wide margins are not necessary. Laparoscopic surgery has been shown to be effective for removal of these tumors without the need of large incisions ***(Nguyen et al., 2006).***

The tyrosine kinase inhibitor Imatinib (Glivec/ Gleevec), a drug initially marked for chronic myelogenous leukemia, was found to be useful in treating GISTs, leading to a 40-70% response rate in metastatic or inoperable cases. Patients who become refractory on Imatinib may respond to the multiple tyrosin kinase inhibitor sunitinib (Sutent) ***(Eisenberg et al., 2009).***

Overall survival (OS) at 5 years for patients with GISTs has been reported to be 19% to 56% from various series. Complete resection has a major effect on survival. This was true even when achieving a complete resection involving the resection of multiple adjacent organs. Tumor grade was the second major factor that had an effect on survival and recurrence. ***(Nguyen et al., 2006).***

Close follow-up with abdominal and pelvic computed tomography scanning beyond the usual 5- year is essential ***(Dematteo et al., 2000).***