Recent Trends in Management of Gastrointestinal Stromal Tumors

Essay

Submitted for the Partial Fulfillment of
Master Degree in **General Surgery**

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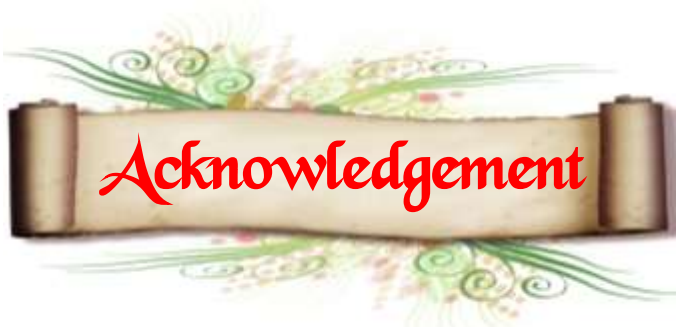
2014



First of all, *thanks to* **Allah** *whose magnificent help was the main factor in completing this work.*

I would like to express my deepest appreciation, respect and thanks to **Prof. Dr. Ibrahim Mohamed Hassanein El-Ghazawy,** *Professor of General Surgery, Faculty of Medicine - Ain Shams University, for his continuous guide in all aspects of life beside his great science, knowledge and information.*

It has been a great honor for me to work under his generous supervision Great words really needed to express my gratitude, sincere appreciation and respect to **Dr. Mohamed Fayek Mahfouz,** *Lecturer of General Surgery, Faculty of Medicine, Ain Shams University, who continued to provide me his guidance ever since. Without his great help, teaching and supervision, this work would not have been completed.*

No words can express my deep sincere feelings Towards **Dr. Moheb Shoraby Eskandaros,** *Lecturer of General Surgery, Faculty of Medicine, Ain Shams University for his continuous encouragement, guidance and support he gave me throughout the whole work. It has been a great honor for me to work under his generous supervision.*

Contents

List of Abbreviations

CML	Chronic myeloid leukemia
CT	Computed tomography
DOG1	Discovered on GIST
EUS	Endoscopic ultrasound
EUS-FNA	Endoscopic ultrasound fine needle aspiration
ESMO	European society for medical oncology
FDG-PET	Flourodeoxyglucose positron tomography
GIST	Gastrointestinal stromal tumor
HPF	High power field
ICC	Interstitial cell of Cajal
MRI	Magnetic resonance imaging
SUVmax	Maximum standardized uptake value
NCCN	National comprehensive cancer network
OS	Overall survival
PR	Partial response
PDGFR-a	Platelet derived growth factor alpha
PET	Positron emission tomography
PET CT	Positron emission tomography computed tomography
PFS	Progression free survival
PD	Progressive disease
RTK	Receptor tyrosine kinase
RFS	Recurrence free survival
SD	Stable disease
SDH	Succinate dehydrogenase gene
TKI	Tyrosine kinase inhibitor

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms accounting for 1-2% of all neoplasms of the digestive tract**.** GISTs were previously considered smooth muscle tumors but are now thought to arise from stem cell precursors of the interstitial cells of Cajal, the neural network that regulates gastrointestinal motility by generating spontaneous electrical slow waves in the gastrointestinal tract ***(Vinay and Gregory, 2011).***

The discovery of the c-kit proto-oncogene, a tyrosine kinase receptor in GIST neoplasms has revolutionized the ability to differentiate these lesions as separate enteties from other mesenchymal, myogenic and neurogenic subepithelial tumors. Immunohistochemical staining for the tyrosine kinase receptor with c-kit (also referred as CD117) has become a definite feature of GISTs and is present in approximately 95% of these lesions ***(Miettinen and Lasota, 2006).***

In most series, gastric tumors are found in 45-65% of the GIST cases followed by tumors of small bowel (15-25%), large bowel including the rectum (5-10%), esophagus (5-10%) and duodenum (3-5%) ***(Machairas et al., 2010).***

The manifestations of GISTs vary widely. Seventy percent of the patients are symptomatic, 20% are

asymptomatic and 10% are detected at autopsy. Of those with symptoms, the majority (35%) are presented with gastrointestinal bleeding. Other presenting symptoms are abdominal pain (32%) and the presence of a palpable mass (13%) **(*Robson et al., 2004*).**

Contrast enhanced computed tomography is the imaging modality of choice for the initial evaluation, staging and monitoring of treatment responses in GIST. Endoscopic ultrasound (EUS) is the most accurate and preferred method of imaging for GISTs. Cytological tissue samples can be obtained through endoscopic ultrasound-fine needle aspiration (EUS-FNA). This technique has the advantage of establishing a diagnosis with reasonable certainty while avoiding the risk of intraperitoneal seedling of the tumor ***(Faigel and Abulhawa, 2012).***

GISTs have a highly variable biological behavior. Although only 10-30% of GISTs are clinically malignant, all GISTs harbor some malignant potential**.** Therefore, primary GISTs are not classified as "benign" or "malignant" but are rather stratified by the probability of recurrence after complete resection. GISTs are stratified into very low, low, moderate and high risk on the basis of their location, size and mitotic rate. Tumor location and size along with mitotic rate (mitosis/50high power field) are reproducible predictors of recurrence risk following complete resection ***(Han et al., 2012).***

The most important prerequisite for an optimal medical care of GIST patients is a multidisciplinary approach to the diagnostic and therapeutic planning. Surgical resection remains the only potential curative treatment for GISTs. The reported respectability rate for localized primary GIST is 70-80%. The high rate of recurrence, even after complete resection, fostered the need for evaluating the role of targeted therapy in the context of adjuvant treatment**.** There is controlled evidence of a benefit for adjuvant imatinib in GIST in terms of both survival and relapse free survival**.** Sumitinib, a multitargeted kinase inhibitor, is effective against imatinib resistant or intolerant GIST patients**.** Novel tyrosine kinase inhibitors including nilotinib and masitinib are in their most mature phase of development ***(Bareck et al., 2013).***

The screening of patients with a predisposition to the development of GIST and surveillance of completely resected GISTs or during neoadjuvent treatment of unresectable GISTs present unique challenges to the surgical and medical oncologist. Flourodeoxyglucose positron emission tomography (FDG-PET) is highy sensitive and specific in response evaluation of GISTs to systemic treatment ***(Choi, 2011).***

Pathology of Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) initially classified as smooth muscle or neural tumors. In 1983, Mazar and Clark introduced the term 'stromal tumor', which became widely accepted in the early 1990's when Miettienen, et al. were able to show the immunohistochemical expression of CD34 in these tumors that was helpful to separate them from leiomyomas, leiomyosarcomas and schwannomas.

1. Epidemiology of GISTs:

Gastrointestinal stromal tumors are rare tumors with an estimated worldwide incidence of approximately 10-20 per million population annually and present 0.1-3 % of all gastrointestinal cancers. It is the most common (80%) mesenchymal tumor of the gastrointestinal tract and represents 5% of all sarcomas. Malignancy possibility is 20-30%. GISTs have a reported incidence of 9 to 14 cases per million per year in most countries in population based studies ***(Blay et al., 2012).***

Estimates of the incidence of GISTs in the USA before 2000 are largely unreliable, primarily arising to inconsistencies in the diagnosis of GISTs. The age-adjusted yearly incidence was estimated to be 0.68/100,000 on the basis

of 1458 cases diagnosed between 1992 and 2000. More accurate estimates, which are based on the rates of accrual onto clinical trials, place the incidence range of 3000 to 6000 new diagnosis annually in the USA ***(Demetri et al., 2010)***.

The yearly incidence of clinically evident GISTs in Europe is approximately 15 cases per one million habitants. However, considering two more recent studies, asymptomatic micro GISTs (0.2-10mm) of the stomach have been reported in up to 35% of Japanese patients, resected of gastric cancer and 22.5% in autopsies of German people above 50 years of age. These minute GISTs often contain an oncogenic mutation in the KIT or PDGFR-a gene comparable to mutations in clinically manifest GIST's ***(Bareck et al., 2013)***.

At the time of diagnosis, the majority of patients with GIST are approximately 60 years old with no clear gender predilection, however, some studies show some increased prevelance in men than women and black races more than white too. Rarely, GISTs occur in children and young adults and these pediatric GISTs are considered as a separate entity and occur predominantly in the second decade ***(Janeway et al., 2007)*.**

Although most GISTs are sporadic, familial GISTs (patients with germ line KIT mutations) are rare, however, well described in the literature. Furthermore, GISTs can also

be associated with hereditary syndromes as neurofibromatosis type I, Carney's triad (gastric GIST, paraganglionoma and pulmonary chondroma) and Carney Startakis syndrome (paraganglionoma and gastric GIST) ***(Hunt et al., 2003)*.**

2- Interstitial Cells of Cajal as the cells of origin:

GISTs are mesenchymal tumors thought to arise from the interstitial cells of Cajal (ICC's), the pacemaker cell of the gastrointestinal tract. In 1990's, the similarities between GISTs cells and the interstitial cells of Cajal were noted. These cells are located in the muscularis propria and around the myenteric plexus and serve as pacemakers for the peristaltic contraction of the gastrointestinal tract ***(Robinson et al., 2000).***

Interstitial cells of Cajal play important roles, such as the mediator of nitric oxide mediated transmission from nerve terminals to smooth muscle cells in the gastrointestinal tract. Simultaneous expression of specific molecules such as KIT, CD34 and nestin in both ICC's and GISTs leads the pathologists to consider that GISTs may develop from ICCs or their progenitor cells ***(Sakurai et al., 2004).***

3-Gross Pathology:

Grossly, GISTs are well demarcated spherical masses that appear to arise from the muscularis propria layer of the

gastrointestinal wall. They often project exophytically and/or intraluminally, and they have overlying mucosal ulcerations. Lager GISTs nearly always outgrow their vascular supply, leading to extensive areas of necrosis and haemorrhage ***(Pidhorecky et al., 2007).***

Small GISTs often form solid subserosal, intramural, or less commonly polypoid intraluminal masses. A majority of larger GISTs form external, sometimes pedenculated masses attached to outer aspect of gut involving the muscular layers. Many larger tumors are centrally cystic and some develop a diverticulum like appearance with the external tumor communicating by the lumen by a fistulous tract. Some GISTs have an asymmetric hour glass like pattern with a smaller internal and a larger external component ***(Miettinen et al., 2005).***

These tumors are usually well circumscribed and generally unencapsulated, though a pseudocapsule maybe present on rare occasions ***(Kale et al., 2008).***