GASTROINTESTINAL STROMAL TUMORS

An Essay
Submitted for fulfillment of the M.Sc. degree in
GENERAL SURGERY

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2012

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that arise from the gastrointestinal tract and account for < 1% of all gastrointestinal neoplasms. ***"van der Zwan , DeMatteo. 2005".***

The term “stromal tumor” was first used by Mazur and Clark in 1983; later the acronym GIST was introduced to define a well established pathological entity, whose constitutive elements derive from the interstitial cell of Cajal, an intestinal pacemaker cell, and express a highly specific marker called KIT (CD117). ***"Miettinen et al. 1995".***

The estimated incidence of GISTs is approximately 10-20 per million people annually worldwide. This tumor affects men slightly more often than women and the mean age at the time of diagnosis is 60 years. The majority of GISTs arise in the stomach (60%) and small bowel (30%); the remaining 10% in the esophagus and rectum. ***"Katz ,DeMatteo . 2008".***

Clinical presentation is heterogeneous, even if GISTs are usually asymptomatic and are diagnosed incidentally during endoscopy, radiological imaging or abdominal exploration. Preoperative biopsy is not recommended for resectable masses, because of the fragility and predisposition to hemorrhage of these masses, and the possibility that the biopsy needle touches a necrotic portion of the tumor. Biopsy is justified only for masses preoperatively judged unresectable, in that a

definitive pathological diagnosis would allow medical treatment using imatinib to commence. ***"Everett , Gutman .2008".***

Surgery represents the gold standard treatment for resectable GISTs. Principles of a correct procedure include negative margins on the specimen and integrity of the pseudocapsule. GISTs do not metastasize through lymphatic spread, so systematic lymphadenectomy is not indicated. ***"Demetri et al. 2007".***

In 2009 the American College of Surgeons Oncology Group presented the results of a randomised Phase III Multicentre Trial that showed the effectiveness of imatinib as adjuvant therapy for primary GISTs in term of recurrence free and overall survival. ***"DeMatteo et al. 2009".***

Acknowledgement

All gratitude is due to ALLAH who guided and aided me to bring-forth to light this essay.

Appreciation and gratitude are due to Prof. Dr. Ahmed Mohamed Lotfy (Professor of General Surgery, Faculty of Medicine, Ain Shams University) for his pioneering supervision, his constant guidance, sincere help, reading circularly the manuscript, and for his continuous encouragement.

Sincere appreciation is expressed to Dr. Ahmed El Sayed Morad(Assistant Professor of General Surgery, Faculty of Medicine, Ain Shams University) for many informative discussions, invaluable assistance, critical review of the manuscript, and continuous help and her facilities.

I have the greatest pleasure in acknowledging Dr. Sherif Abd El-Halim (Lecturer of General Surgery, Faculty of Medicine, Ain Shams University) for help at all stages of preparation of the manuscript, his intrepid and unfailing pursuit of the research and his scientific astuteness.

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Aim of the work

The aim of this work is to provide a review of literature about the anatomical locations , histological, pathological consideration of gastrointestinal stromal tumors and, its management.

Abbreviations

ALK	Anaplastic Lymphoma Kinase
BID	Twice Daily
DFS	Disease free survival
EUS	Endoscopic ultrasonography
EGIST	Extra Gastrointestinal Stromal Tumors
GANTs	Gastrointestinal autonomic tumors
GI	Gastrointestinal
GIT	Gastrointestinal tract
GIST	Gastrointestinal stromal tumor
GIST/Ls	Gastrointestinal stromal tumors and leiomyomas
GIPACTs	Gastrointestinal pacemaker cell tumors
JM	Juxtamembrane
HAE	Hepatic Artery Embolisation
HPF	High Power Field
IM	Imatinib Mesylate
ICCs	Interstitial cells of Cajal
LMP	Low malignant potential

MVD	Microvessel density
NSE	Neuron Specific Enolase
OD	Once daily
OS	Overall survival
PD	Progressive disease
PR	Partial response
PFS	Progression-free survival
PDGFRα	Platelet-derived growth factor receptor alpha
PFS	Progression-free survival
RR	Response rate
SCF	Stem Cell Factor
SMemb	Embryonic isoform of myosin heavy chain
SMA	Smooth muscle actin
SU	Sunitinib
SUVmax	Maximum standardized uptake value
TAP1	Telomerase-associated protein 1
TAUS	Transabdominal Ultra
VEGFRs	Vascular endothelial growth factor receptors

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HISTORICAL BACKGROUND

OF GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumours (GIST), the most common mesenchymal tumour of the gastrointestinal tract, are predominantly found in middle-aged or older adults with an incidence rate of 6.5-14.5 per million per year**."*Nilsson et al.2005***"

Since the term GIST was introduced by Mazur and Clark in 1983, laboratory investigations aimed at the subcellular and molecular levels ,have demonstrated that GISTs do not possess the ultrastructural and immunohistochemical features characteristic of smooth muscle differentiation, as are seen in leiomyomas and leiomyosarcomas. Therefore, the determination was made that GISTs do not arise from smooth muscle cells, but from another mesenchymal derivative such as the progenitors of spindle and epithelioid cells. ***"Mazur, Clark .1983"***

According to the work of Kindblom and associates reported in 1998, the actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cell of Cajal.These are GI pacemaker cells and are largely responsible for initiating and co-ordinating GI motility. This finding led Kindblom and coworkers to suggest the term GI pacemaker cell tumors. Perhaps the most critical

development that distinguished GISTs as a unique clinical entity was the discovery of c-***kit*** proto-oncogene mutations in these tumors by Hirota and colleagues in 1998." ***Hirota et al,1998***"

GIST occurs mostly in the stomach (60%–65%) or small intestine (25%–35%) but can arise anywhere along the gastrointestinal tract***." Nikfarjam et al,2008***"

It is mostly a rare sporadic tumor seen in older adults (median age 55–60 years). Familial GIST is rare but can be seen in patients with neurofibromatosis type I (multiple small intestinal tumors) or Carney's triad (gastric epithelioid GIST, pulmonary chondroma, and extra-adrenal paraganglioma). Histologically, 95% of GISTs express the transmembrane receptor CD117, which is the main immunohistological marker." ***Miettinen ,Lasota .2006***"

In tumors lacking a *kit* mutation approximately 35% have a gain-of-function mutation of the platelet-derived growth factor receptor alpha, a related tyrosine kinase receptor. A tyrosine kinase inhibitor for c-kit. GISTs are, finally, defined as pleomorphic mesenchymal tumors of the GI tract that express the KIT protein (CD 117- Protooncogene that encodes the transmembrane tyrosine kinase receptor CD 117 detected by flow cytometry in most cases of acute myeloid leukemia, in small numbers of T- and B-lymphoblastic lymphomas, and in some gastrointestinal stromal tumors- stem cell factor receptor) and often also CD34 (human progenitor cell antigen) on immunohistochemistry." ***Corless et al,2004***"

The clinical behavior of GISTs can vary from a benign to a highly aggressive course. The 2 main prognostic factors are the mitotic activity and the size of the tumor. More than 5 mitoses per 50 high-power fields (HPF) and size greater than 10 cm are almost uniformly identified as factors associated with poor outcomes after surgery." ***Rutkowski et al,2007***"

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 is resistant. Indeed, surgical resection was historically the only therapy with demonstrated, albeit short-term, efficacy in true GISTs. However, even complete surgical resection of primary GIST carried a substantial risk for recurrence, Surgery alone rarely resulted in a cure. **"*Charles, Blanke.2004*"**

However surgical resection of the local disease is the gold standard therapy. Its goal is complete resection of the disease with avoidance of tumor rupture." ***Verweij et al,2004***"

Conventional chemotherapy for the treatment of GIST has a dismal response rate of approximately5 %." ***Demetri et al,2002***"

During the period of time that Imatinib has not been used for GIST therapy, the 5 year survival after the surgical resection was only 40-75%.

The median survival of recurrent GIST after resection was 15 months in the pre-Imatinib era." ***Tsukuda et al,2007"***

The prognosis of low risk GIST after complete resection was excellent, but the prognosis of high risk GIST was low and the rate of recurrence with 5 year survival ranged from 0% to 30%. However, after the introduction of molecular targeted therapy, Imatinib, there is a major improvement in the survival." ***Ponsaing et al,2007***"

Gupta and his coworked follow-up the patient with physical examination every 3-4 months for 2 years, then every 6 months for the next 2 years, then yearly. Chest X-ray and abdominal CT scan and blood test were obtained yearly." ***Gupta et al,2008***"

Flexible upper endoscopy is performed at 6 months and 1-year postoperatively and then annually for 2 years. PET (positron emission tomography) scanning of abdomen, MR (Magnetic Resonance) imaging, or chest CT scan is done if abnormalities are found in any of the surveillance studies." ***Safdar et al,2007***"