Recent Modalities in Management of Gastrointestinal Stromal Tumours

Essay
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List of Abbreviations

Abbrev.	*Full Term*
AIDS	Aquired immunodeficiency syndrome.
BID	Twice daily.
CB	Clinical benefit .
CGH	Comparative genomic hybridization.
CML	Chronic myeloid leukemia or Chronic myelogenous leukemia.
C_{min}	Plasma concentration.
CR	Complete response.
DFS	Disease free survival.
DOG 1	Discovered on GIST 1.
EUS	Endoscopic ultrasonography.
GANTs	Gastrointestinal autonomic tumors.
GI	Gastrointestinal.
GIT	Gastrointestinal tract.
GISTs	Gastrointestinal stromal tumors.
GIST/Ls	Gastrointestinal stromal tumors and leiomyomas,
GIPACTs	Gastrointestinal pacemaker cell tumors.
JM	Juxtamembrane.
HAE	Hepatic arterial embolization.
HPF	High power field.
HTERT	Human telomerase reverse transcriptase.
HTR	Human telomerase RNA component.
ICCs	Interstitial cells of Cajal.

List of Abbreviations (cont.)

IM	Imatinib Mesylate.
LMP	Low malignant potential.
MVD	Microvessel density.
OD	Once daily.
OS	Overall survival.
PD	Progressive disease.
PDGFRα	Platelet-derived growth factor receptor alpha.
PFS	Progression-free survival.
PR	Partial response.
RECIST	Response Evaluation Criteria in Solid Tumors .
RR	Response rate.
SD	Stable disease.
SMemb	Embryonic isoform of myosin heavy chain.
SMA	Smooth muscle actin.
SU	Sunitinib.
SUVmax	Maximum standardized uptake value.
TAP1	Telomerase-associated protein 1.
VEGFRs	Vascular endothelial growth factor receptors.

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Introduction

Gasrtointestinal stromal tumours(GISTs) are neoplasms that arise from either mesenchymal tissue of gastrointestinal tract or from other intraabdominal soft tissue. They arise from stem cell called interstitial cell of Cajal. ***(Corlos et al., 2005).***

GIST occur any where along gastrointestinal tract most commonly in the stomach and small intestine and less commonly in the colon and rectum. ***(Jonsuu, 2012).***

The malignant potential of GIST ranges from small lesions with benign behavior to malignant sarcoma. 40% of GIST tumours that are localized at time of detection give rise to metastasis. ***(Emile,2012).***

Although patients have symptoms or a palpable tumour at presentation ,25%of GIST discovered incidently during surgery or imaging for other disorders. The most frequent symptoms are abdominal pain , bleeding in bowel, dyspepsia or vomiting. ***(Nilsson et al., 2005).***

Endoscopic contrast enhanced ultrasound is valuable for assesssment of large gastric, duodenal and rectal GISTs, Imaging by CT or MRI is usually needed. ***(Jonsuu, 2012).***

Surgery is the mainstay of therapy for a primary non-metastatic GISTs ,but probability of recurrence depends on

tumor characterestics. Following removal of primary GIST, patients at risk of recurrence need adjuvant therapy with Imatinib. Patients with metastatic GIST, even if removed ,definitely need drug treatment to maintain tumour control. Lymph node metastasis are 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 on removal of these tumors without the need of large incisions.***(Nguyen et al., 2006).***

The c-kit 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).***

Aim of the Work

The aim of this work is to discuss and review the recent modalities in management of gastrointestinal stromal tumours.

Pathology of GIST

GISTs account for 5% of all soft tissue sarcomas, predominantly occur in middle aged and older patients (fifth to seventh decades). The cell of Cajal is the cell of origin of Gist.Gist can be classified into benign,malignant and low malignant according to its site ,size and mitotic activity ***(Sullivan et al., 2006).***

Incidence of Gist:

GISTs account for 5% of all soft tissue sarcomas, predominantly occur in middle aged and older patients (fifth to seventh decades) ***(Barnes et al., 2005).***

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).***

Cells of Origin of Gist "ICCS":

The cells of Cajal are intercalated between the autonomic nerves and the muscle layers of the gastrointestinal tract, functioning as gastrointestinal pacemaker cells that are important for the autonomous intestinal motility ***(Anthony et al., 2005).***

ICCs play important roles, such as the pacemaker that enables cooperative peristalsis or 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, the embryonic isoform of myosin heavy chain (SMemb), and nestin in both ICCs and GISTs leads to consider that GISTs may develop from ICCs or their progenitor cells ***(Shinji et al., 2004).***

Multifocal hyperplasia of interstitial cells of Cajal has been described as precursor of hereditary GIST in patients with germline mutations in c-KIT and PDGFRA (*platelet-derived growth-factor receptor, alpha polypeptide),* with GIST tumorlets (microscopic GIST) being the counterpart caused by somatic mutations in c-KIT or PDGFRA in patients with sporadic GIST***(Agaimy et al., 2007).***

Aetiology and Risk Factors of Gist:

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. Most GISTs occur in older patients, typically between the ages of 50-60. Sporadic instances are rare before