Recent Trends in The Management of Gastrointestincal Stromal Tumours

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الجديد في علاج أورام الخلايا السدية للجهاز الهضمي

بحث
مقدم توطئة للحصول على درجة الماجستير في
الجراحة العامة

مقدم من
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بكالوريوس الطب والجراحة

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Abbrev	
FDG	Fluorodeoxyglucose
ACK2	Anti-KIT monoclonal antibody
ACOSOG	American College of Surgeons Oncology Group
ATP	Adenosine triphosphate
CIIP	Chronic intestinal pseudo-obstruction
CT	Computed tomography
EORTC	European Organization for Research and Treatment of Cancer
GISTs	Gastrointestinal stromal tumors
HPFs	High powered fields
ICC	Interstitial cells of Cajal
IHC	Immunohistochemistry
ITDs	Internal tandem duplications
KL	KIT ligand
MAP	Mitogen activated protein
MRI	Magnetic resonance imaging
PDGFR	Platelet derived growth factor receptor
PET	Positron emission tomography
RECIST	Response Evaluation Criteria in Solid Tumours
STC	Slow transit constipation
VEGFR	Vascular endothelial growth factor receptor

Introduction

Gastrointestinal stromal tumors (GISTs) are a subset of soft tissue sarcomas that develop primarily along the gastrointestinal tract and often spread within the abdomen. While GISTs account for only 0.2% of all gastrointestinal tumors, 80% of all gastrointestinal sarcomas are GISTs. The prognosis for GIST has traditionally been notoriously poor, with a dearth of effective therapies. However, clinical management of GIST patients has changed dramatically ***(Choi, 2008)***.

GISTs are the most frequent non epithelial neoplasms of the gastrointestinal tract, with a preferred gastric localization (about 60% in the stomach and 20–30% in the intestine). The median age of onset is 60–69 years and the symptoms are usually non-specific such as tiredness, abdominal discomfort and gastro-intestinal bleeding. The main instruments used for the diagnosis of GISTs are CT scans and PET scans ***(Spinelli et al., 2008)***.

Clinical studies have shown that the elective medical treatment for patients with inoperable lesions is imatinib (400 mg/die) with positive responses above 50%. The use of other treatments such as Sunitinib, another tyrosine kinase inhibitor, has been approved in patients who do not respond to treatment with imatinib, and generally present a mutation of the exon 9 of c-kit ***(Siehl and Thiel, 2007; Fletcher and Rubin, 2007)***.

Tumor size significantly correlated with mitotic count; larger tumors usually had higher mitotic counts and were frequently unresectable. As a result, GIST cases with tumor size > 10 cm have poorer survival ***(Yan et al., 2003)***. These two histologic criteria are important to define the biological behavior of a tumor and risk category for prognosis. Conventional histologic factors do not predict the malignant potential and malignant actions of GISTs. Recently, the descriptors of the malignant behavior of GISTs, benign and malignant, were substituted with low, intermediate, and high risk. Such results confirm that prognosis is significantly better for patients in very low, low-, and intermediate-

risk categories than for patients in high-risk categories ***(Mucciarini et al., 2007)***.

Complete tumor resection is another important factor related to survival ***(Bucher et al., 2004)***. ***Mucciarini et al. (2007)*** reported that for GISTs with metastasis or with incomplete resection, survival was poor after surgery alone. After radical surgery, the majority of relapses occurred in patients with tumors classified as high risk. It seems to be no differences between the three lower risk categories when tumor is resectable while limited differences can be found when considering metastatic events in all patients. These distinction and obviously limitations due to the small number of patients should all be considered when comparing outcome of intermediate risk category in this study with other series.

Aim of the Work

This essay aims to discuss the various types of GIST, incidence, prognosis with special emphasis on the new trends in management.

Genetics and Pathogenesis of GIST

Digestive motility is highly coordinated and consists of local, non-propulsive mixing (segmental) and propulsive (peristaltic) movements. Mixing movements are produced by intrinsic pacemakers generating rhythmic contractions and peristalsis by intrinsic excitatory and inhibitory neural reflex pathways ***(Stevens et al., 1999)***.

Even in the absence of stimulation, most regions of the gastrointestinal tract can generate some spontaneous electrical and mechanical activity. Recordings made from isolated muscle cells in the gastrointestinal tract show a regular discharge recorded as plateau and slow potentials. These pacemaker potentials are generated by a specialized population of cells, known as interstitial cells of Cajal (ICC) ***(Ward, 2000)***.

Together with the enteric nervous system, composed of both the myenteric (inter-muscular) plexus

and the submucosal plexus, the ICC plays a major role in gastrointestinal motility ***(Takaki, 2003)***.

The ICC was firstly described by Cajal SR in 1911. He characterized "interstitial neurons" as "primitive accessory components that could modify smooth muscle contraction, subject themselves to regulation from principal neurons". Cajal provided detailed pictures of methylene blue-stained networks of interstitial cells, which were described as spindle shaped or stellate cells with long, ramified cell processes and large, oval nuclei with sparse perinuclear cytoplasm, and intercalated between autonomic nerve endings and smooth muscle cells ***(Cajal, 1995).***

ICC constitutes networks that are widely distributed within the submucosal, intra-muscular and inter-muscular layers of the gastrointestinal tract from the lower esophagus to the internal anal sphincter. These cells are defined by the expression of the CD117 (c-kit) protein which is a membrane receptor with tyrosine kinase activity ***(Long et al., 2004)***.

I. ICC in small intestine and colon:

A. Idiopathic chronic intestinal pseudo-obstruction (CIIP):

CIIP is characterized by defective gastrointestinal propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions or mechanical obstacle ***(De Giorgio et al., 2004a)***. CIIP is regarded as a neuropathy, myopathy or both ***(De Giorgio et al., 2004b)***.

A possible role played by the ICC is demonstrated by the alterations in ICC network reported in patients with CIIP. Electron microscopy and immunochemistry studies showed a decreased number of ICCs along with structural abnormalities such as loss of processes and damaged intracellular cytoskeleton and organelles ***(Feldstein et al., 2003)***.

B. Slow transit constipation (STC):

This is a very prevalent motility problem, but its mechanisms are unclear. Studies found that ICC density

in the colon of patients with constipation was significantly decreased compared with those of normal patients ***(Basilisco et al., 2005)***. Expression of c-kit mRNA and c-kit protein was significantly decreased in the colon of STC, suggesting that the c-kit signal pathway may play an important role in ICC reduction in STC ***(Tong et al., 2005)***.

Since slow-transit constipation is secondary to problems with the ENS, ICC, or smooth muscle cells, replacement of the missing or defective cells would be an attractive way of treatment ***(Schiller, 2004)***. Growing precursors of the defective cells from stem cells should be easy, but the distribution of the cells to their proper locations is still problematic. For the moment this is a promise of genetic treatment ***(Rao, 2003)***.

II. Tumors of gastrointestinal tract:

Gastrointestinal stromal tumors (GISTs):

GISTs have been recognized as a biologically distinctive tumor type, different from smooth muscle and

neural tumors of the gastrointestinal tract. They constitute the majority of gastrointestinal mesenchymal tumors ***(D'Amato et al., 2005)***.

GISTs originate from the ICC. Their origin from the ICC has been proven by their immunophenotypic (CD117 positive) and ultrastructural resemblance and also by the presence of an embryonic smooth muscle myosin similar to the one present in the ICC **(Table 1)**. Approximately 80% of GISTs also express CD34 ***(Hwang and Kimmey, 2004)***.

Annual incidence of clinically detected new cases of GISTs in the United States has increased to 5000-6000 per year due to better diagnosis, and incidence is rising. Uncommonly, GISTs arise in families, and in these patients germline mutations of c-kit have been identified particularly in exons 11 and 13. A diffuse hyperplasia of the ICC, which is regarded as a pre-neoplastic lesion is noted in these patients. The patients with exon 11 mutations develop cutaneous mastocytosis with or without cutaneous hyperpigmentation, but those with exon 13 mutations do not have these features

(D'Amato et al., 2005). The tumors under 3 cm in diameter are mostly benign, but all GISTs have a malignant potential ***(Hwang and Kimmey, 2004)***.

The term stromal tumor was first introduced by ***Mazur and Clark (1983)*** to define a group of gastric mesenchymal tumors that were not clearly differentiated by immunohistochemistry and ultrastructure and that were previously thought to be derived from smooth muscle of the gastrointestinal wall.

In 1998, ***Kindblom et al. (1998)*** and ***Hirota et al. (1998)*** independently determined that these neoplasms are significantly immunoreactive for CD117, a polyclonal antibody recognizing the type III tyrosine kinase KIT, which is encoded by the proto-oncogene c-kit.

Since in the normal gastrointestinal tract KIT is exclusively expressed by the interstitial cells of Cajal (ICC), specialized cells that interact with neural and muscular structures that have a pacemaker activity, the authors suggested that gastrointestinal stromal tumors (GISTs) might derive from ICC or from stem cells