NOVAL STRATEGIES OF GASTROINTESTINAL STROMAL TUMOR

Essay

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By

Mohamed Atef El Azazy
M.B, B.Ch
Faculty of Medicine,
Ain Shams University

Supervised By

Prof. Dr. Amr Abd El Raouf Abd El Nasser
Professor of General Surgery
Faculty of Medicine Ain Shams University

Dr. Mostafa Abdo mohamed
Lecturer of General Surgery
Faculty of Medicine Ain Shams University

Faculty of Medicine
Ain Shams University
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LIST OF ABBREVIATIONS

Abbrev.	Full term
ABL	Abelson's Tyrosine Kinase
Akt	AKT1 protein kinase Human homolog of v-akt oncogene product
ATP	Adenosine triphosphate
AUC	area under the curve
BCR-ABL	B Cell Antigen Receptor
BRAF	Serine/threonine protein kinase activating the MAP kinase signaling pathway
BRAF V600E mutation	BRAF mutations
CD117	Cluster designation 117
CD34	CD34 molecule is a cluster of differentiation (designation) molecule
CML	Chronic myeloid leukemia
CT	Computed tomography
DOG1	Discovered on GIST- 1
EGIST	Extra-gastrointestinal stromal tumors
EM	Electron microscopy
ESMO	European society for medical oncology
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
FDG-PET	18 fluoro-deoxy-glucose PET scan
FLT3	Fms-like tyrosine kinase-3 receptor
GANT	Gastrointestinal autonomic nerve tumor
GIST	Gastrointestinal stromal tumor
GI	Gastrointestinal
HPF	High Power Field
ICC	Interstitial cells of Cajal
KIT or c-KIT	Tyrosine kinase receptor or Mast/stem cell growth factor receptor (SCFR), also known as proto-oncogene (c-Kit) or tyrosine-protein kinase (Kit) or CD117
MAP kinase	Methyl Adenosine Phosphoryl kinase
MRI	Magnetic resonance imaging

LIST OF ABBREVIATIONS *(cont's)*

Abbrev.	Full term
MRP1	Multi drug resistance protein 1
NCCN	National comprehensive cancer network
NF1	Neurofibromatosis type 1
PDGFRA	Alpha-type platelet-derived growth factor receptor
PET scan	Positron emission tomography scan
PKC-theta	Protein-C kinase theta
RET	The ret proto-oncogene
RFA	Radiofrequency ablation
SD	Segmental duodenectomy
SDH	Succinate dehydrogenase
SMA	Smooth muscle actin
SMTs	Submucosal tumors
TKI	Tyrosine kinase inhibitor
U/S	Ultrasound
U.S.	United states
VATS	Video- assisted thoracoscopic surgery
VEGF-R1, -R2, -R3	The vascular endothelial growth factor receptor isoforms

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Mohamed Atef El-Azazy

INTRODUCTION

Following descriptions in the 1940s by Stout and others, stromal tumors arising from the gastrointestinal tract were classified as smooth muscle neoplasms. These rare tumors were classified as various entities including leiomyosarcoma, leiomyoblastoma and bizarre leiomyoma, until, at least, the 1960s. ***(Yagihashi et al., 1987)***.

With the advent of electron microscopy (EM) in the late 1960s, smooth muscle features were seen only in occasional GIST cells, raising into question the smooth muscle origin of this entity. In addition, several authors reported ultrastructural features reminiscent of autonomic nerve structures, with schwannian and neuroaxonal characteristics, in tumor specimens microscopically indistinguishable from GIST ***(Yagihashi et al., 1987)***.

With the introduction of immunohistochemistry in the early 1980s, it was soon appreciated that many of these tumors lacked immunophenotypic features of smooth muscle, and conversely, a proportion of tumors stained positively for S-100 protein, a marker for neuroectodermal differentiation. This led Mazur and Clark to suggest the myenteric nervous system as a possible cell of origin and to introduce a more generic term, "stromal tumor" ***(Mazur and Clark, 1983).***

In 1989, a distinctive subset of gastrointestinal tumors showing autonomic neural features was described and termed “plexosarcoma” and subsequently became better known as gastrointestinal autonomic nerve tumor (GANT). ***(Lauwers et al., 1993).***

By the early 1990s, there was considerable confusion as to the lines of differentiation of these tumors. Some were obviously neurogenic, some myogenic, others displayed bidirectional differentiation and a subgroup with null phenotype. To further complicate matters, there was a distinct lack of histologic prognostication methods, with great difficulty classifying GIST even into benign and malignant categories. Tumors showing the usual histologic criteria for malignancy did not uniformly behave aggressively, and on the other hand, some tumors with benign features gave rise to metastases ***(Lauwers et al., 1993).***

From 1994, it became apparent that a significant proportion of GANT were immunopositive for CD34, and for a while CD34 was hailed as the marker for GIST. This finding also raised the possibility that GIST might be related to the interstitial cells of Cajal ICC on the basis of CD34 immunopositivity. Interstitial cells of Cajal, sometimes

known as the pacemaker cells of the gastrointestinal tract, form the interface between the autonomic nervous system and the smooth muscle. They possess the immunophenotypic and ultrastructural characteristics of both the neural and smooth muscle elements. ***(Nagata et al., 1996).***

However, over the next several years, it also became apparent that not more than 70% of GIST cases were truly positive for CD34. This was further confounded by the fact that Schwann cell, and other smooth muscle tumors, were also variably CD34 positive, thus obviating the diagnostic efficacy of CD34. ***(Nagata et al., 1996).***

Up until 1998, it was unclear what the cell of origin GIST derived from, how best to accurately diagnose GIST, or even to distinguish malignant from benign GIST. In parallel to developments in GIST, by the mid-1990s, various reports emerged describing gain-of-function mutations, and consequently, constitutive activation of Tyrosine kinase (KIT) receptors in several human tumor mast cell lines ***(Nagata et al., 1996).***

Finally in 1998, in a landmark publication, Hirota and colleagues made two key discoveries: a near-universal expression of KIT in GIST and the presence of activating *C-KIT* mutations in GIST. In Hirota's series of 49 GIST samples, 94% of cases expressed KIT. Mutations in the juxtamembrane domain of C-KIT were detected in five of six

samples of GIST, resulting in constitutive ligand-independent activation of the KIT receptor tyrosine kinase. The oncogenic role of KIT was confirmed when stable transfection of the mutant C-KIT cDNAs induced malignant transformation of murine lymphoid cells. In addition, 82% (40 of 49) of GIST were CD34-positive and 78% (38 of 49) were positive for both CD34 and KIT. ICC were also found to be positive for both KIT and CD34, suggesting close morphologic relations between ICC and GIST. In the same year, work by Kindblom and colleagues corroborated findings from Hirota and colleagues, showing that 78 of 78 SIST studied were immunoreactive for KIT, and shared striking ultrastructural and immunophenotypic similarities with ICC. This work again supported the hypothesis that GIST may indeed develop from stem cells that differentiate toward ICC phenotype and confirmed KIT as an accurate diagnostic tool for GIST ***(Kindblom et al., 1998).***