REVIEW

Classification of gastrointestinal stromal tumor syndromes

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, thought to derive from neoplastic outgrowth of the interstitial cells of Cajal. Building on recent advances in recognition, classification and diagnosis, the past two decades have seen a changing paradigm with molecular diagnostics and targeted therapies. *KIT* and *PDGFRA* mutations account for 85–90% of GIST carcinogenesis. However, the remaining 10–15% of GISTs, which until recently were called *KIT*/*PDGFRA* wild-type GISTs, have been found to have one of the several mutations, including in the *SDHA*, *B*, *C*, *D*, *BRAF* and *NF1* genes. Though most of such GISTs are sporadic, a number of families with high incidence rates of GISTs and other associated clinical manifestations have been reported and found to harbor germline mutations in *KIT*, *PDGFRA*, *SDH* subunits and *NF1*. The goal of this review is to describe the mutations, clinical manifestations and therapeutic implications of syndromic and inherited GISTs in light of recent studies of their clinicopathologic range and pathogenesis.

Key Words
- GIST
- imatinib
- *KIT*
- *PDGFRA*
- *NF1*
- *SDHx*

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) system (Boikos & Stratakis 2014), with more than 5000 newly diagnosed cases yearly in the United States (Barnett *et al.* 2013). The incidence of these tumors is variable from as low as 4.3–6.8 per million to as high as 19–22 cases per million, with a high degree of variability between different geographic areas (Soreide *et al.* 2016). The reported median age is in the mid-60s in most studies (Soreide *et al.* 2016); the stomach is the most frequent primary site, involving ~55%, followed by small intestine (~30%) and rectum (~5%) (Barnett *et al.* 2013, Soreide *et al.* 2016). Rarely, GISTs arise in other GI locations or appear clinically to arise as primary tumors in other viscera.

Historically, smooth muscle was considered the tissue of origin of GISTs, given the predominant spindle cell histomorphology and frequent expression of smooth muscle cell markers (Schroeder *et al.* 2016). In the late 1990s, a key finding in GISTs was the discovery of their similarity to the interstitial cells of Cajal, specialized stromal cells which serve as the pacemaker for the GI tract by integrating neurotransmitter and other signals to coordinate smooth muscle cell contractions. c-KIT protein (also known as CD117), which is commonly expressed both on interstitial cells of Cajal and GISTs, is a crucial

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driver of tumor growth (Hirota *et al.* 1998, Kindblom *et al.* 1998). The *KIT* gain-of-function mutation is well established as the molecular driver of a majority of GISTs, while expression of the c-KIT protein provides a standard of care diagnostic marker (Hirota *et al.* 2000). Besides *KIT* mutations, GISTs have been found to harbor mutations in other genes, including platelet-derived growth factor (PDGF) receptor alpha (*PDGFRA*), succinate dehydrogenase complex subunits (*SDHx*), neurofibromin 1 (*NF1*), B-raf proto-oncogene (*BRAF*) and most recently, epigenetic changes 'epimutation' of *SDHC*. An even smaller subset of until recently unclassified GISTs is now known to harbor even rarer mutations, including *PI3K3CA*, *CBL* and *KRAS*.

Most of the GISTs are sporadic, but in approximately 5% of the patients, GIST is part of one of several familial syndromes. These syndromes include Carney–Stratakis syndrome (CSS), Carney triad, neurofibromatosis type 1 and primary familial GIST syndrome (Carney & Stratakis 2002, Mussi *et al.* 2008, Agarwal & Robson 2009, Forde *et al.* 2016). Recently, it had been shown that CSS and Carney triad are characterized by mutations and methylation changes, respectively, of *SDH* subunit genes, leading to global SDH deficiency, while neurofibromatosis-associated and familial GIST syndrome tumors remain SDH-competent.

These rare hereditary GISTs, several having distinctive clinical features and characteristic genomic alterations only well appreciated in recent years, are the subject of this review. From the standpoint of organization, in this review, discussion of GIST syndromes will be organized along the two aforementioned overall molecular classes of GISTs (SDH-competent and SDH-deficient). While these two molecular groups are often used to describe GISTs generally (irrespective of whether they have documented syndromic features or germline mutation), they importantly correspond to groups that may have specific, targetable oncogenic mutations, especially among the SDH-competent GISTs. While in contrast, the emerging group of SDH-deficient GISTs presently has less clear targeted therapies, they imply specific surveillance recommendations and differing treatment pathways, emphasizing that a precision medicine approach is standard of care even among different groups of syndromal GISTs.

SDH-competent familial GISTs (mutations in *KIT*, *PDGFRA* or *NF1*)

KIT-mutated syndromic GISTs

The landmark discovery of activating mutations of c-KIT in GISTs was reported in 1998 (Hirota *et al.* 1998). It is now well established that 75% of the GISTs harbor *KIT* mutations, and subsequent pharmacologic findings have proven that it is a clinically important therapeutic target. *KIT* encodes the c-KIT receptor tyrosine kinase, a type III tyrosine kinase receptor, which is the receptor of stem cell factor (SCF). The binding of SCF ligand induces c-KIT dimerization, which induces receptor activation and downstream signaling mobilization, including through the PI3K/AKT and RAS pathways (Bauer *et al.* 2007). Contemporary understanding of the molecular pathogenesis of GISTs underscores that *KIT* mutation and its dependent signaling pathways are the hallmark of GISTs and distinct from other sarcoma types.

Beyond the vastly more common sporadic GISTs with somatic mutation of *KIT*, recent studies have established that rare familial GIST cases are related to heritable germline mutations of *KIT* (Forde *et al.* 2016). In fact, to date more than 31 families and 6 individuals have been found to have germline mutations in *KIT*, most often in exon 11 but also in exons 8, 9, 13 and 17 (Ricci 2016). Consistent with its oncogenic function, the inheritance pattern in these families is autosomal-dominant, and the youngest reported age of GIST diagnosis is 15, with median age of 40–50 (Li *et al.* 2005, Kleinbaum *et al.* 2008). These families have often other clinical manifestations, including achalasia, melanoma, multiple lentigines, perioral and perineal hyperpigmentation and urticaria pigmentosa. GISTs in these patients tend to have spindle cell histology and can be seen anywhere in the GI tract, including the esophagus, stomach and small bowel. *KIT*-mutated GISTs (whether somatic or germline) tend not to metastasize to lymph nodes. There are neither major differences as compared to sporadic *KIT*-mutated GISTs in terms of medical and surgical treatments, nor a clear female predominance. However, consistent with the presence of constitutional (germline) *KIT* mutations being present in every cell, affected individuals demonstrate diffuse hyperplasia of their interstitial cells of Cajal. This is a unique feature, contrasting the other germline mutations associated with GIST development, and providing supportive evidence of the defining role of c-KIT activation in the hereditary and sporadic settings.

Two years after the discovery of activating *KIT* mutation in GISTs, imatinib was identified as a potent antagonist of c-KIT in the cellular model (Heinrich *et al.* 2000). Only one year after this *in vitro* study, a favorable outcome was reported in a case report (Joensuu *et al.* 2001). Not surprisingly, the subsequent large cohort clinical trial achieved great success by using imatinib

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(Demetri *et al.* 2002). In familial *KIT*-mutated GISTs, response to imatinib can be variable, based on the specific tumor genotype.

PDGFRA-mutated syndromic GISTs

Of sporadic GISTs that do not harbor somatic *KIT* mutations, *PDGFRA* is the most common oncogenic mutation. PDGFRA is a type III tyrosine kinase receptor, a close homolog of c-KIT, functioning physiologically as the receptor of several PDGF isoforms (Joensuu & DeMatteo 2012). *PDGFRA* mutation induces constitutive kinase activation and interacts with c-KIT. Consistent with their functional overlap, these mutations are mutually exclusive in GISTs (Heinrich *et al.* 2003*b*, Hirota *et al.* 2003, Corless *et al.* 2011). Quite analogous to the aforementioned observation of kindreds with germline *KIT* mutation and predisposition to GISTs, recently a rare, familial counterpart of sporadic *PDGFRA*-mutant GISTs has been identified (Ricci *et al.* 2015). Three families and one individual have been described harboring germline *PDGFRA* mutations; the clinical manifestations in these families are variable, including lipomas, fibrous tumors in the GI tract and large hands (Chompret *et al.* 2004, Pasini *et al.* 2007, Carney & Stratakis 2008).

Overall, *PDGFRA* mutations in GISTs cluster in exons 12 (juxtamembrane regulatory domain), 14 (tyrosine kinase domains-ATP-binding region) and 18 (activation loop). Interestingly, PDGFRA-mutant GISTs have mostly epithelioid histology; they arise primarily in the stomach. Usually, patients with *PDGFRA*-mutated GISTs tend not to have metastases to lymph nodes. Specifically in *PDGFRA*-mutant syndromal GISTs, there is a strong female predominance (Ricci 2016). Contrasting somewhat the finding in kindreds affected by germline *KIT* mutation, patients with *PDGFRA* germline mutations never have diffuse hyperplasia of interstitial cells of Cajal, instead of having only focal hyperplasia (Chompret *et al.* 2004).

Beyond the rare scenario of *PDGFRA* mutation-related hereditary GISTs, in *PDGFRA*-mutated GISTs generally, the mutation type is associated with important clinical and therapeutic outcomes. Mutations in exons 12, 14 and 18 demonstrate variable response to imatinib, sunitib and regorafenib (Jakhetiya *et al.* 2016). Most of the *PDGFRA* mutations have been identified in exon 18, which is believed to stabilize the kinase activation loop (Dibb *et al.* 2004). The most frequent single mutation, the *PDGFRA* mutation, c.*2525A>T* causing the amino acid substitution D824V, occurs in 70% of all *PDGFRA* mutations and 5% of metastatic GISTs (Corless *et al.* 2005). It is considered as the most common mutation conveying primary resistance to imatinib (Heinrich *et al.* 2003*a*), and median survival is only 12.8 months compared with 48–60 months on average for imatinib-treated GISTs (Corless *et al.* 2011). Due to this primary resistance to imatinib or sunitinib, alternative approaches, including dasatinib or crenolanib, have been used and are thought to have greater activity (Heinrich *et al.* 2012). Fortunately, the *PDGFRA* mutation, c.*2525A>T*, despite being the most common *PDGFRA* mutation in sporadic GISTs, has never been reported in the germline mutants.

Neurofibromatosis type 1 (NF-1)

NF-1 is an autosomal-dominant tumor syndrome that is caused by mutation of the *NF1* gene located on chromosome 17. It is characterized by café-au-lait spots, neurofibromas, pheochromocytoma and in some cases, GISTs. NF-1 is relatively common, with 1:4–5000 prevalence, and has complete penetrance but variable expression in terms of its broad clinical manifestations. Approximately 7% of the patients develop a GIST during their lifetime (Zoller *et al.* 1997). The median age of GIST diagnosis in NF-1 patients is 49. NF-1-related GISTs are located in the small bowel, are often multifocal, have a spindle cell morphology and often a background of Cajal cell hyperplasia (Wada *et al.* 2016). NF-1 patients can also have other GI tumors like neuroendocrine tumors (including somatostatinomas arising from the ampulla). NF-1 syndromal GISTs are usually small with a low mitotic rate and generally good prognosis, though 15–20% of the NF-1-related GISTs can be aggressive (Wang *et al.* 2011). There is no clear female predominance in these patients. From a therapeutic standpoint, NF-1-related GISTs have not responded well to imatinib (Mussi *et al.* 2008). While there is no reported efficacy of imatinib, there is a report of a response to sunitinib (Kalender *et al.* 2007). Currently, there is an ongoing trial at the US National Institutes of Health designed to target NF-1-related GISTs through MEK inhibition (NCT03109301).

The prognosis of NF-1-associated GISTs is controversial. In one cohort, reported by Miettinen *et al.*, these patients enjoyed an overall good prognosis, with only five out of 35 patients dying of metastatic disease (Miettinen *et al.* 2006). Conversely, two case reports have stated that NF-1-mutated GISTs either only showed an initial response to imatinib (Lee *et al.* 2006) or were completely resistant to imatinib (Mussi *et al.* 2008). Of note, these studies have substantial discrepancy of tumor-proliferative status, mitotic count and tumor size, which may explain the

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different outcomes. We emphasize that greater experience will be necessary in this area, and the role of adjuvant treatment with imatinib in NF-1 syndromal cases remains debatable (Mussi *et al*. 2008).

SDH-deficient GISTs (*SDHA*, *B*, *C*, *D* mutations, *SDHC* epimutants)

The SDH complex

The succinate dehydrogenase (SDH) complex, also known as complex II, is a heterotetrameric enzymatic complex composed of A, B, C and D subunits, located in the inner mitochondrial membrane (Gill 2012). The SDH complex physiologically plays a role in both the Krebs cycle and the respiratory chain. Mutation in any of the subunits leads to instability of the complex and degradation of SDHB subunit protein. For that reason, loss of SDHB expression, as detected by immunohistochemistry (IHC), is being increasingly used as a marker for the SDH-deficient phenotype, which can subsequently be clarified by genetic studies (Gill *et al*. 2010). SDH deficiency leads to intracellular succinate accumulation, which inhibits a broad family of enzymes that are called dioxygenases, including propyl-hydroxylases, JmjC domain-containing histone demethylases (KDMs) and the TET family of dioxygenases (Killian *et al*. 2013, Boikos *et al*. 2014, Wang *et al*. 2015) (Fig. 1). Inhibition of prolyl-hydroxylases leads to hypoxia-inducible factor (HIF) 1a stabilization, inducing constitutive pseudohypoxic signaling and consequent upregulation of expression of several oncogenes. Inhibition of TET and KDM family enzymes leads to DNA and histone hypermethylation, respectively (Yang & Pollard 2013).

Collectively, these changes are thought to drive tumorigenesis in the multiple organ systems that demonstrate increased incidence of neoplasia in individuals harboring germline *SDHx* mutations, which include paragangliomas/pheochromocytomas, GISTs and, among a subset, a histologically distinctive type of renal cell carcinoma (Gill *et al*. 2014, Williamson *et al*. 2015). Importantly, with regard to GISTs, SDH-deficient GISTs can be due to either genetic (*SDHA*, *B*, *C* or *D* mutations) or epigenetic (*SDHC* promoter methylation) changes. In principle, they can be either sporadic, due to somatic mutations within the tumor, or familial, related to germline mutations, though at present the vast majority are thought to be familial. In terms of classic descriptions of syndromal features, there are 2 distinctive but related syndromes that have SDH-deficient GISTs as a defining feature, Carney triad and CSS (Boikos *et al*. 2014, 2016*a*).

Carney triad

Carney triad was first described in 1977, as a triad of gastric leiomyosarcomas (now understood to be GISTs), paragangliomas and pulmonary chondromas (Carney *et al*. 1977). Carney triad has also been reported to be associated with esophageal leiomyoma and adrenal cortical adenoma; the overall course in affected individuals tends to be indolent (Carney 1999). The GISTs in Carney triad are essentially always gastric in location and tend to be multifocal, with epithelioid histology and a plexiform growth pattern (Chetty & Serra 2016). In a report by the US NIH, it was shown that 95% of the affected patients are female, with a median age at presentation of 22 years (Zhang *et al*. 2010). In 2007, in a study of 37 patients with Carney triad, a 1q12-q21 deletion was identified as the most frequent and largest contiguous change, a region notably subtending the locus of the *SDHC* gene (Matyakhina *et al*. 2007). However, *SDHx* point mutations were not found at this time in affected individuals. For this reason, in 2011 it was proposed that patients with no *SDHx* mutations but with loss of SDHB by IHC should be considered as Carney triad patients (Gaal *et al*. 2011).

Later, studies revealed that at this same chromosomal locus 1q12-q21, patients with Carney triad had hypermethylation of the promoter of *SDHC* and consequently reduced mRNA expression of *SDHC*, providing further evidence implicating this locus. Killian *et al*. then confirmed these results, performing genome-wide DNA methylation profiling and demonstrating that six of the 15 Carney triad patients had *SDHC* epimutation (Haller *et al*. 2014, Killian *et al*. 2014). Finally, very recently, *SDHx* mutations were found in patients with Carney triad, suggesting that the various SDH-deficient syndromes overlap significantly (Boikos *et al*. 2016*b*).

Carney–Stratakis syndrome

CSS was first described in 2002, as a syndrome of familial gastric GISTs and paragangliomas, which was described as separate from Carney triad (Carney & Stratakis 2002). CSS is inherited as an autosomal-dominant syndrome with incomplete penetrance, such that affected patients may have either the complete CSS with GIST and paragangliomas or incomplete CSS with only GIST, being at risk to develop paragangliomas in the future. Patients are at risk, more rarely, also for other tumors such as renal

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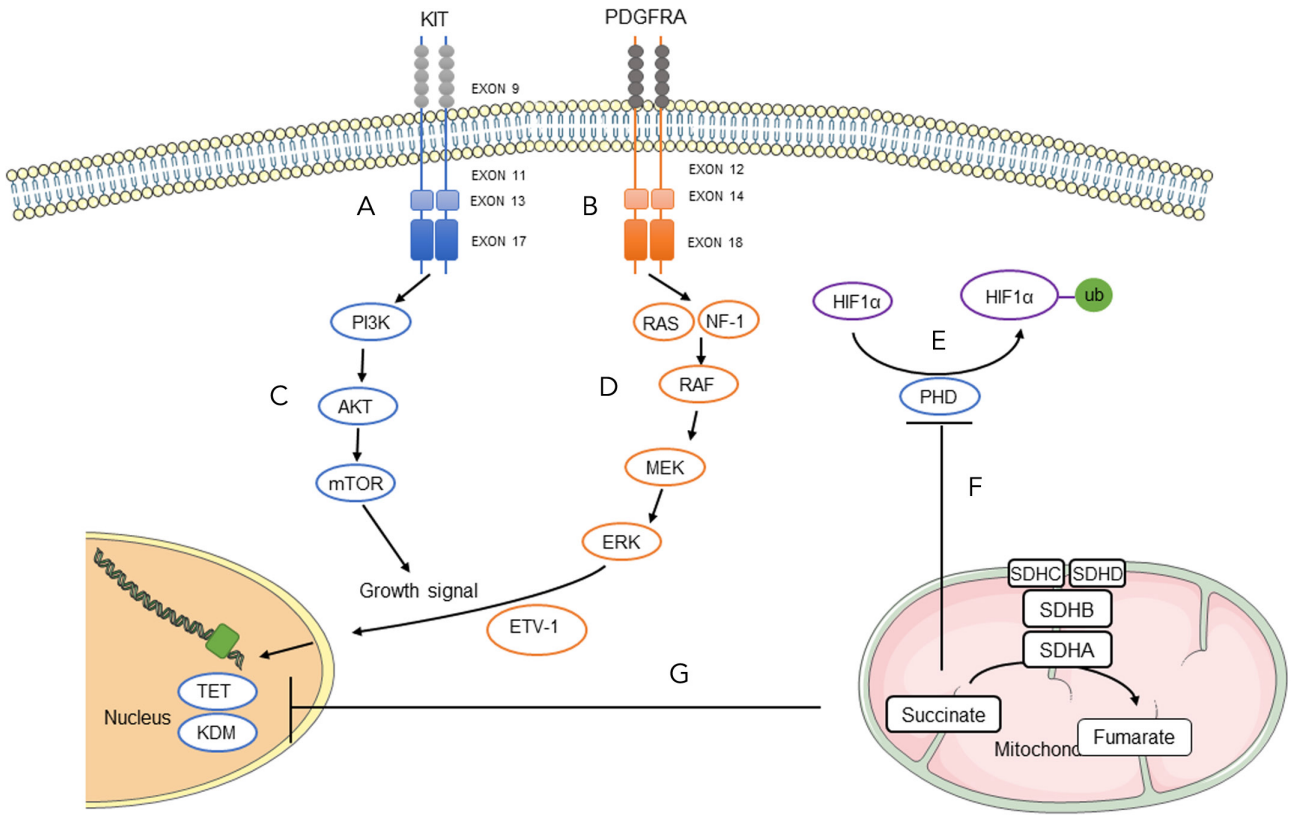

Figure 1
Oncogenic molecular pathways in gastrointestinal stromal tumor (GIST). (A) The most common mutations in *KIT*-mutated GIST are exon 11 (juxtamembrane domain), exon 9 (extracellular domain), exon 13 (ATP-binding pocket) and exon 17 (activation loop). (B) The most common mutations in *PDGFRA*-mutated GIST are exon 18 (activation loop), exon 12 (juxtamembrane domain) and exon 14 (auto-inhibitory part of juxtamembrane domain). (C) Mutation of *KIT* or *PI3K* leads to constitutive activation of PI3K–AKT–mTOR pathway, resulting in enhanced growth signaling. (D) Mutation of *PDGFRA*, *NF1*, *BRAF* or *RAS* leads to mobilization of RAS–RAF–MEK–ERK pathway. Together with *ETV1*, these signals cause induced activation of proliferation. (E) Under normoxic conditions, hypoxia-inducible factor (HIF) 1a undergoes degradation by prolyl-hydroxylase domain (PHD) protein-mediated hydroxylation via ubiquitination. (F) Succinate dehydrogenase (SDH) is a mitochondrial enzyme (heterotetrameric, complex II). Subunits A/B are catalytic proteins localized on mitochondrial inner membrane, and subunits C/D are anchoring components. Inactivated mutation of these subunits causes accumulation of intracellular succinate, which competitively inhibits PHD proteins. Subsequent elevation of HIF-1a activity stimulates hypoxic signaling and associated tumorigenesis. (G) Succinate accumulation leads to inhibition of TET and KDM enzymes and global DNA and histone methylation changes, respectively.

cell carcinomas. These patients usually have a gastric-based multifocal GIST, epithelioid histology and median age in their third decade (Wada *et al.* 2016). In terms of the molecular pathogenesis of the syndrome, constitutional inactivating mutations of *SDHB*, *SDHC* or *SDHD* have been confirmed in the vast majority of CSS patients (Benn *et al.* 2006, McWhinney *et al.* 2007). Additionally, the syndrome of pituitary adenomas, paragangliomas and pheochromocytomas (3PAs) has also been reported to be associated with *SDH* subunit germline mutations (Xekouki *et al.* 2015).

Notably, however, the SDH-deficient GISTs arising in these syndromes have been noted to have poor responses to traditional imatinib therapy (Pasini *et al.* 2008). This overall poor response rate is thought to relate to the lack of the activating tyrosine kinase mutations that drive tumorigenesis as in SDH-competent (whether syndromal or sporadic) GISTs with *KIT* or *PDGFRA* mutations. Subgroup analysis of the EORTC phase III trial 62005 (imatinib in patients with unresectable/metastatic GISTs) reported that those with 'wild-type' (with respects to *KIT* and *PDGFRA*) GISTs (a group enriched for SDH-deficient GISTs) had a 76% increased relative risk of death compared with patients with *KIT* exon 11 mutant GISTs (Debiec-Rychter *et al.* 2006).

Therefore, broader multitarget kinase inhibitors have emerged as future treatment candidates. Of note, in a human study of the SDH-deficient GIST subpopulations, the *SDHA*-mutated subset presented an impressively long survival with the use of sunitinib after imatinib (Pantaleo *et al.* 2015). In a phase I/II study which had included a total of 97 metastatic, imatinib-resistant GISTs, of which

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9 were wild-type GISTs, sunitinib was more active in *KIT* exon 9 mutant and wild-type GISTs than *KIT* exon 11 mutations (Heinrich *et al*. 2008). In the group of treatment failures after imatinib and sunitinib, administration of regorafenib showed significant activity, with median PFS of 12 months (George *et al*. 2012). Likewise, pazopanib demonstrated a potential response in heavily pretreated patients, though only five wild-type GIST patients were recruited in this phase II study (Ganjoo *et al*. 2014). In the adjuvant setting, subanalyses of wild-type GISTs in both the ACOSOG Z9001 trial (Corless *et al*. 2014) (32 patients) and the SSGXVIII (19 patients) (Joensuu *et al*. 2012) did not detect any benefit. A recent report from the NIH pediatric and wild-type GIST clinics further supports the contention that disease progression was largely dependent on tumor biology, regardless of location and resection margins. Most patients survive with disease progression, indicating that wild-type GIST is an overall indolent disease (Weldon *et al*. 2016). Additionally, particularly for SDH-competent syndromic GISTs with germline oncogenic mutations, at present there are no data to suggest that they should be treated any differently, with regard to adjuvant/neoadjuvant therapy, than their sporadic counterparts.

As many wild-type GISTs overexpress the IGF receptor 1, the SARC-022 phase 2 trial tested a new TKI, linsitinib, which results in significant inhibition of IGF receptor 1. Preliminary findings were not very promising, as no objective response could be observed. PFS at 9 months was 52% (Mehren *et al*. 2014), though final reporting for this trial is still pending. There are currently 2 ongoing studies, specific for SDH-deficient tumors: one using the glutaminase inhibitor CB-839 (NCT 02071862) and another employing a new-generation DNA methyltransferase inhibitor, guadecitabine (SGI-110).

Recommendations for familial/syndromic GISTs

Patients with GIST and clinical features suggesting a type of syndromic/inherited GIST, as summarized in Table 1, should be offered an appropriate germline testing for the specific clinical phenotype. Once mutation is identified in any of the *KIT/PDGFRA/SDH A, B, C, D/NF1* genes, appropriate local and systemic treatment should be chosen, and genetic testing should be offered to first-degree relatives.

There are no special surgical recommendations for familial *KIT/PDGFRA/NF1*-mutated GISTs, as distinct from sporadic GIST with such mutations. However, in contrast, patients with SDH-deficient GISTs tend to have limited benefit from an extensive or repeated surgery, since surgery in these patients has limited clinical benefit due to prevalent early metastases, the overall multifocal nature of the tumors and the nonetheless paradoxically indolent course of the disease. In a recent report from NIH, presenting the follow-up data in a cohort of 76 patients, the 5- and 10-year event-free survival was 23.7 and 16.3%, respectively (Weldon *et al*. 2016). Surgery in SDH-deficient GIST patients seems not to have a curative role, and the recommendation is that surgery should be considered primarily in the palliative setting, in cases of pain, obstruction or GI hemorrhage.

Postoperative surveillance with computed tomography scan or ^{18}F-FDG PET CT has been suggested

Table 1 Syndromic GIST.

Type	Gene	Age	Sex	Pathology, site	Genetics	Features
KIT-germline mutation	*KIT* exon 8, 9, 11, 13, 17	40–50	N/A	S>E, stomach/small bowel	AD/HP	Various proliferation rate, ICC hyperplasia/motility disorder, skin pigmentation, sporadically non-GIST tumors
PDGFRA germline mutation	*PDGFRA* exon 12, 14, 18	40–50	N/A	M/E>S, stomach	AD/HP	Inflammatory fibroid polyp, GI lipoma, no ICC hyperplasia, large hands observed
NF type 1	*NF-1*	49	N/A	S>M, small bowel	AD/HP, variant expression	Café-au-lait spots, neurofibroma, freckling, paraganglioma, ICC hyperplasia/motility disorder
Carney's triad	*SDHC* promoter hypermethylation	~15	F>M	E>S, stomach	N/A	Paraganglioma, pulmonary chondroma, adrenal cortical adenoma
Carney–Startakis syndrome	SDH_x-mutation	~23	F>M	E>S, stomach	AD/IP	Paraganglioma

AD, autosomal-dominant; E, epithelioid; HP, high penetrance; ICC, interstitial cell of Cajal; IP, incomplete penetration; M, mixed; S, spindle cell.

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previously every 3–6 months for surveillance of syndromic GIST. Patients with SDH-deficient GISTs, who have a more indolent course and are being diagnosed at a younger age, should be scanned primarily with MRI in order to minimize radiation exposure. Patients with SDH-deficient GISTs should also have annual whole-body MRI and urine or plasma catecholamines in order to detect paragangliomas. Other imaging modalities that have been used for paragangliomas are ^{68}Ga-DOTATATE, ^{18}F-DOPA and ^{18}F-FDA (Ricci 2016). Similar modalities should be used for carriers with *SDHx* mutations, since they are at risk to develop GIST or paragangliomas. Upper GI endoscopy with ultrasound and associated biopsy is important for biopsy and diagnosis but has a limited role for surveillance purposes.

The role of systemic treatment in various GIST syndromes has been discussed in previous sections of this review for each GIST syndrome, given the substantial differences between them. However, it is generally evident that imatinib has a very limited role in SDH-deficient GISTs, while in the other syndromes, the response to imatinib is variable, according to the specific genotype.

Summary

As the first solid tumor being treated by target therapy, the success in the past decade in treatment of GISTs is based on the growing understanding of its basic molecular biology. Though GISTs still represent a highly heterogeneous group of tumors, with much to learn in both their sporadic and syndromal/familial forms, the predictive and prognostic value of mutation status in this disease has become widely accepted as standard of care. Given that the genotype of each individual GIST has a substantial impact on treatment response, prognosis and drug resistance, the current translational goal is to provide ever more personalized regimens incorporating the mutational status of a GIST, key histologic and clinical staging factors and even such emerging data as secondary mutations. The concepts of leveraging high-throughput molecular data to propose combination therapies or structure/function analysis of individual mutations for novel target discovery are quickly becoming foreseeable, rather than just aspirational, goals on the horizon. Intriguingly, observations from these differing groups of familial and syndromic GISTs have confirmed in human kindreds the central importance of many of the driver mutations seen (and now targeted therapeutically) in the more common sporadic GISTs. We suspect that in the coming years, studies of the syndromic GISTs, especially the SDH-deficient group, will continue to drive forward the science and treatment of this disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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