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SDH-deficient gastrointestinal stromal tumours

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Gastrointestinal stromal tumours (GIST) comprise a heterogeneous group of the most common mesenchymal neoplasms of the gastrointestinal tract. The majority of GIST are induced by activating, mutually exclusive mutations of two genes – *KIT* and *PDGFRA* (platelet-derived growth factor receptor-alpha). However, approximately 10–15% of GISTs lack oncogenic *KIT* or *PDGFRA* mutations and these tumours are often called "wild type" (WT) GISTs. The SDH-deficient GISTs form a distinctive subset of tumours accounting for 20–40% of *KIT/PDGFRA* WT GIST, which results from the loss of function mutations in the genes encoding the SDH enzyme complex. The true frequency of SDH-deficient GISTs was reported to be approximately 7.4 to 7.7%. These tumours usually occur in the stomach (most commonly in the antrum) and have a spectrum of behaviour from indolent to progressive. In most cases the molecular mechanism behind the SDH-deficient GISTs is connected to germline mutations. *SDHA* germline mutations occur in approximately 30% of the SDH-deficient GIST, those in *SDHB*, *SDHC*, and *SDHD* appear in 20–30% of patients.

The SDH-mutated GISTs do not respond well to the commonly used targeted therapy, with no objective tumour response to imatinib. Taking into account the biological features of SDH-deficient GIST, new therapies of potential interest comprise PI3K/AKT/mTOR inhibitors, heat-shock protein inhibitors, HIF1-α targeting agents, epigenetic modifiers and demethylating agents. However, further research is necessary in these fields.

Key words: gastrointestinal stromal tumour, SDH-deficient GIST, Carney Triad, Carney-Stratakis syndrome, TKI, *SDHA/SDHB/SDHC/SDHD* mutations, targeted therapy, imatinib, regorafenib

Introduction

Gastrointestinal stromal tumours (GIST) comprise a heterogeneous group of the most common mesenchymal neoplasms of the gastrointestinal tract. Most GIST are related to activating, somatic, mutually exclusive mutations of two genes – *KIT* and *PDGFRA* (platelet-derived factor receptor-alpha), which are early oncogenic events during GIST development [1–3]. Advances in the understanding of molecular events underlying GIST tumorigenesis have led to an awareness of the essential role of KIT and PDGFRA oncoproteins as diagnostic and therapeutic targets, and to the paradigm for molecularly targeted therapy. However, approximately 10–15% of GISTs lack oncogenic *KIT* or *PDGFRA* mutations and these tumours are often called "wild type" (WT) GISTs (fig. 1) [4–5]. They are indistinct from *KIT/PDGFRA*-mutated tumours in terms of morphology, anatomic localization and the expression of two diagnostic immunohistochemical markers (KIT and DOG-1). Importantly, from a molecular point of view and based on their succinate dehydrogenase (SDH) immunohistochemical status, WT GISTs are heterogeneous group of tumours that can be classified

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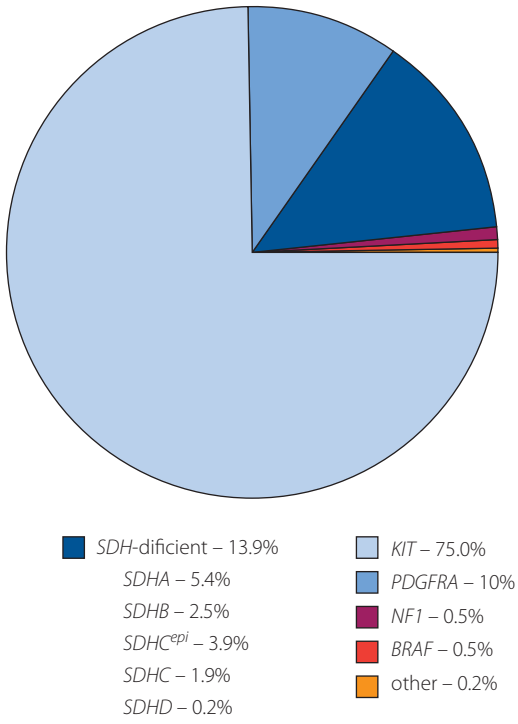
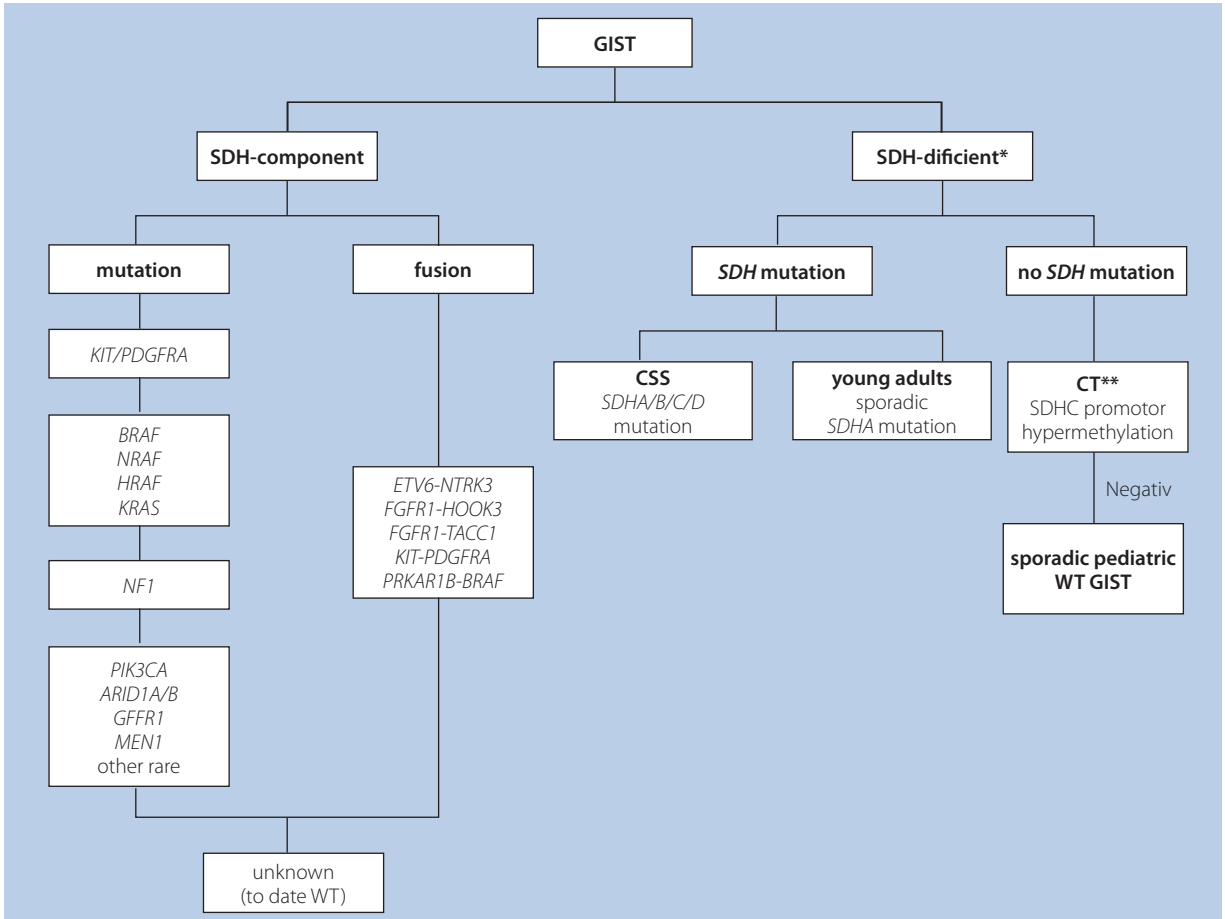


Figure 1. Molecular subtypes in GIST. Based upon Schaefer et al. [6]

into two main subtypes: SDH-competent and SDH-deficient tumours (fig. 2) [6–8]. The SDH-competent group constitutes mainly GIST related to neurofibromatosis type 1 (von Recklinghausen disease) [9, 10], but also includes rare tumours that carry oncogenic fusions of neurotrophic tyrosine kinase (*NTRK*), *BRAF* and fibroblast growth factor receptor (*FGFR*) genes [12, 13], as well as more aggressive and occurring in older patients WT GISTs harbouring somatic mutations in *NF-1, BRAF, NRAS, HRAS, KRAS, EGFR1, MAX, MEN1*and *PIK3CA* genes [10, 14, 15]. In some of these WT cases (especially paediatric), overexpression of the insulin-like growth factor 1 receptor (IGF1R) has been observed [16].

Clinical and molecular features of SDH-deficient GISTs

SDH-deficient GISTs form a distinctive subset of tumours accounting for 20–40% of *KIT/PDGFRA* WT GIST, which results from the loss of function mutations in the genes encoding the SDH enzyme complex. The true frequency of SDH-deficient GISTs was reported to be approximately 7.4 to 7.7% [17, 18]. These tumors comprise the majority of pediatric GISTs, a low percentage of sporadic cases, and two classes of syndromic GISTs – Carney triad and Carney-Striatakis syndrome [5, 7, 8,



CT – Carney traid; CSS – Carney-Stratakis syndrome; SDH-defiecient* – screening by immunohistochemistry; CT** – in some cases mutation described; SDH – succinate dehydrogenase; GIST – gastrointestinal stromal tumours

Figure 2. SDH-component and SDH-deficient sub-classification of GISTs [4, 9]

19, 20]. They are characterized by a predominant location in the stomach, multifocality, propensity for lymphatic spread and often indolent clinical behaviour even in metastatic disease [21, 22].

SDH-deficient GISTs usually develop early in childhood and in adolescents/young adults [2]. However, patients in their forties or fifties may also emerge with an initial diagnosis of SDH-deficient GIST. Females are reported to be disproportionately affected. SDH-deficient GISTs usually occur in the stomach (most commonly the antrum) and have a spectrum of behaviour from indolent to progressive. The summary of the main characteristics of SDH-deficient GIST is presented in table I and II. Over 80% of pediatric GIST has inactivating mutations in SDH subunits [23, 24].

Succinate dehydrogenase (SDH, also known as mitochondrial complex II or succinate-ubiquinone oxydoreductase) is a highly conserved heterotetrameric enzyme complex (composed of four protein subunits – SDHA, SDHB, SDHC, and SDHD, encoded by nuclear genes, mapped to 5p15.22, 1p36.13, 1q23.3 and 11q23.1, respectively), which acts at the interphase of the tricarboxylic acid cycle and electron transport chain. SDH is the only enzyme that is concurrently both a functional member of both the Krebs cycle and the electron transport chain (ETC), where it provides electrons for oxidative phosphorylation [24].

The SDH-complex takes part in the Krebs cycle with subunit A (SDHA), a flavoprotein, which is the catalytic unit responsible for the conversion of succinate to fumarate, and Subunit B (SDHB), which is an iron-sulfur- protein participating in the electron transport chain for the oxidation of ubiquinone to ubiquinol. Together SDHA and SDHB make up the main catalytic component of the complex, while the other two subunits (SDHC and SDHD) are two integral membrane proteins, anchoring the complex to the inner mitochondrial membrane [25]. Additionally, the succinate dehydrogenase assembly factor 2 (SDHAF2) is required for the flavination and thus normal function of SDHA [26].

Genetic or epigenetic alterations in any of the subunits lead to an accumulation of succinate, which is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases (including the TET family of 5-methylcytosine hydroxylases). Members of the TET family are active DNA demethylases that convert 5-methylcytosine to 5-hydroxymethylcytosine, and inhibition of their activities can lead to aberrant DNA methylation observed in GISTs [27]. A genome-wide DNA methylation analysis of SDH-deficient GISTs revealed higher DNA hypermethylation than in GISTs with *KIT* mutation [28].

Carney triad (CT) is a very rare disease characterized by the synchronous or metachronous occurrence of at least three different tumour entities, i.e GIST, paraganglioma and pulmonary chondroma [29]. Carney triad is never inherited, affects mostly females and the symptoms occur in young adults. Most cases of CT show down-regulation of SDH through site-specific hypermethylation (epigenetic downregulation) of the SDHC gene [27], which leads to downstream activation of the HIF signalling pathway by accumulation of succinate, causing stabilization of HIF1-α that controls oncogene transcription. Activated cellular pathways leading to increased angiogenesis and cellular proliferation are activated [31].

Table I. Summary of the main characteristics of SDH-deficient GIST

Characteristics	
clinical	• rare • more often developing in young patients and women • commonly developing in the stomach and small intestine • more often diagnosed in emergency settingsprimary resistance to imatinib is common • GIST with *SDH* mutations tend to metastasize, including to the lymph nodes and less frequently to the liver, usually growing slowly • indolent growth causes that standard risk classifications do not apply to SDH-deficient GIST • many are related to hereditary syndromes, i.e. Carney triad or Carney-Stratakis syndrome
pathological	• frequently epithelioid/mixed morphology, SDHB loss detected by immunohistochemistry, regularly express KIT and its pathway is activated, insulin-like growth factor 1 receptor (IGF1R) is overexpressed
molecular	• *KIT/PDGFRA* wild type, loss of function mutations in *SDHA*, *SDHB*, *SDHC* or *SDHD* in approximately 80% of cases

Table II. Anatomic distribution, frequency and treatment response of the SDHB-immunonegative/SDH-deficient GISTs

Genetics	Frequency	The most frequent anatomic location	Systemic treatment
SDHB IHC(–)/SDH-deficient *SDHA/B/C/D* mutations (CSS)	2%	stomach	• limited responses to imatinib • possible response to other TKIs (limited data)
part of the CT *	1%	stomach	
SDHA mutation (young adults)		stomach	
sporadic paediatric WT GIST	1%	stomach	

CSS – Carney-Stratakis Syndrome; CT – Carney triad; * – most cases show promotor hypermethylation

Carney-Stratakis syndrome (CSS) is characterized by gastric multifocal GISTs and paragangliomas [19], showing an autosomal dominant inheritance pattern with incomplete penetrance. It affects both males and females during childhood and adolescence. Succinate dehydrogenase deficiency is caused by inactivating germline mutations or large deletions in the *SDHB*, *SDHC* or *SDHD* (rarely *SDHA*) genes encoding the corresponding subunits B, C or D of the SDH enzyme [29, 32, 33].

In contrast to CT, in patients with CSS, DNA methylation patterns were identified only at a few of the CpGs located close to the *SDHB* gene [27]. In these patients, the *SDHC* gene promoter was completely unmethylated in all screened CpG sites, supporting the hypothesis that the CSS is in fact a different entity from CT [28].

The most practical way to identify the loss of SDHB is to find SDH-deficient tumours with the use of immunohistochemistry (IHC) [17]. Immunohistochemical expression of SDHB becomes negative whenever there is bi-allelic inactivation of any component of SDH, which is very rare in the absence of syndromic disease[35]. Unfortunately, only approximately 30% of SDH-deficient GISTs demonstrate loss of expression for SDHB and SDHA by IHC. Furthermore, tumours with loss of SDHB expression by IHC can be subdivided into 2 groups: tumours with *SDH* gene mutations and those with a loss of SDHB by immunostaining but without *SDH* mutations. Those with *SDH* mutations occurring in young adults are gastric in location, and have a female preponderance [8].

Loss of function of the succinate dehydrogenase complex characterizes other rare human tumours including some paragangliomas, renal carcinomas and pituitary adenomas. Along with GISTs, they can all be characterized as SDH-deficient tumours [36]. From a histopathological perspective, SDH-deficient GISTs show characteristic morphologic features including a multinodular growth pattern, the occurrence of multiple tumours, lymphovascular involvement and lymph node metastasis [37].

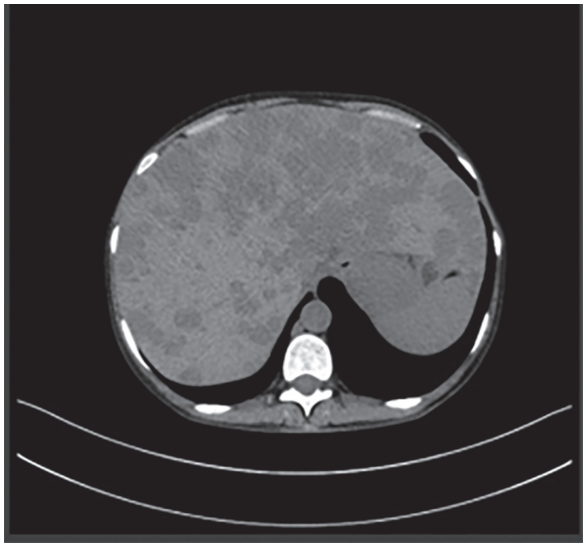


Figure 3. Computed tomography imaging demonstrating SDH-deficient gastric GIST with extensive liver metastases

Liver metastases are common (fig. 3). Morphologically, these tumours are epithelioid or mixed epithelioid/spindled [34].

The molecular mechanism behind the SDH-deficient GISTs is connected to germline mutations. Germline mutations in *SDHA* occur in approximately 30% of the SDH-deficient GIST, those in *SDHB*, *SDHC* and *SDHD* occur in 20–30% of cases (tab. III) [34, 36–38].

The most common *SDHA* mutation detected in SDH-deficient GISTs patients is the c.91C>T (p.Arg31Ter) substitution. Simultaneous allelic loss at the *SDHA* locus at 5p15 has been described; in this scenario the tumour follows a classic 2-hit hypothesis, with SDHA acting as tumour suppressor [8, 41, 42]. The loss of SDHA protein expression may result

Table III. *SDHA/B/C/D* mutations detected in SDH-deficient GISTs [5, 32, 33, 39, 41, 42]

Gene	Exon	Mutation
SDHA	2	c.113A>T c.91C>T
	4	c.356G>A
	5	c.457-2_457del c.512G>A
	6	c.628C>T c.698G>T c.770G>C
	9	c.1151C>G
	12	c.1663+3G>C
	13	c.1754G>A c.1766G>A
	14	c.1799G>A
SDHB	1	c.17 42dup
	2	c.137G>A
	3	c.274T>A
	4	c.380T>G c.423+1G>A c.423+20T>A
	6	c.600G>T
	7	c.725G>A
SDHC	1	c.1A>G c.6delT
	4	c.380A>G c.301delT c.224G>A
	5	c.397C>T c.405+1G>A
	6	c.455G>C
SDHD	1	c.34G>A polymorphism
	4	c.416T>C c.352delG

from both truncating and missense germline mutations. *SDHA*-mutation associated GISTs occur at an older age than other SDH-deficient GISTs, with a median age of 34 years at presentation [39, 40].

SDHB-, *SDHC*-, and *SDHD*-mutation associated tumours occur in a minority of cases (20–30%). Most of these *SDH* mutations are germline. Approximately 20% of patients with these SDH subunit mutations also develop paragangliomas [5, 41]. The remaining 50% of the SDH-deficient GIST (without a germline *SDHA/B/C/D* variants) are caused by CpG island hypermethylation in the promoter region of the *SDHC* gene, which is also referred to as a "*SDHC* epimutation" [28, 40]. *SDHC* epimutations can be associated with Carney's triad as previously described [43]. The lifetime penetrance of GIST in asymptomatic *SDH* genes mutation carriers is not known [36].

Therapy

SDH-deficient GISTs behave as an indolent disease and most patients survive with disease progression with a median survival time of 10 years[44]. Studies have found that current risk stratification criteria might not be appropriate for use on this type of GIST [22]. Despite low overall mortality, disease progression and recurrence occur frequently. The results of a retrospective analysis from the NIH Pediatric and Wild-type GIST clinic reported in 2017 revealed that 76 WT GIST patients, who underwent surgery, had a median event-free survival (EFS) of 2.5 years, with 71% of patients experiencing tumour recurrence or disease progression [44]. The EFS was negatively impacted by an elevated mitotic index and the presence of metastases. Noteworthy, negative resection margins and neoadjuvant or adjuvant treatment did not appear to affect EFS. The localized cases of SDH-deficient GIST should be treated with surgery as it is the essential and only potentially curative modality. All surgical decisions should be individualized and morbidities weighed against the benefits of resection. Generally, in SDH-deficient GIST with pathologically enlarged nodes, lymphadenectomy must be considered, but in cases of multifocal disease, extensive surgery (as total gastrectomy) related to significant morbidities is not recommended to reduce the risk of recurrence in the stomach [45]. In GIST patients with SDH-deficiency, the risk of paraganglioma is increased and diagnostic tests should be considered prior to surgery.

The role of adjuvant therapy with imatinib in even the theoretically higher risk group of this GIST subtype is not established, as WT GIST have no confirmed benefit from postoperative imatinib therapy.

The introduction of imatinib mesylate, a small-molecule selective inhibitor of receptor tyrosine kinase, has revolutionized the therapy of advanced (inoperable and/or metastatic) GIST [46, 75], and subsequently imatinib was applied in adjuvant therapy after resection of high risk GIST [47]. In cases of GIST progression on imatinib therapy, the commonly used strategy is to introduce alternative molecular targeted agents such as sunitinib, regorafenib and ripretinib [48–50]. Nevertheless, *KIT* and *PDGFRA* mutational status strongly correlates with the response and progression-free survival (PFS) in GIST patients treated with imatinib. It has been observed that systemic treatment in metastatic WT GIST showed no objective tumour response to imatinib, and superior response to sunitinib, especially in the pediatric GIST group [51]. That said, there was still an inferior response to all tyrosine kinase inhibitors when compared to KIT-mutated GIST [40]. Specifically, SDH-deficient tumours are not well recognized in terms of sensitivity to tyrosine kinase inhibitors in large phase II and III clinical trials. As mentioned previously, it is implied that SDH-mutated GISTs do not respond well to the commonly used targeted therapy, with no objective tumour response to imatinib [8]. Reliable clinical research on pure populations of SDH-deficient GIST is uncommon because these tumours are rare, and they are well identified relatively recently. These factors, together with the commonly observed slow growth of these tumours, make collection of reliable data concerning their natural clinical course and biology, as well as their response to drugs, very difficult, as time lapses of apparent disease stability could be independent of the drug activity [52, 53].Interestingly, a subgroup analysis in the EORTC phase III trial 62005 with the use of imatinib has demonstrated that *KIT/PDGFRA* wild-type GIST patients had a 76% greater risk of death compared with *KIT* exon 11 mutants [54]. In phase I/II study in 97 patients with metastatic imatinib-resistant GISTs (including nine WT GIST patients), sunitinib was shown to be more active in *KIT* exon 9 mutations and WT GISTs compared with *KIT* exon 11 mutations. In another study, a potential response to pazopanib (an inhibitor of KIT, PDGFRA, VEGFR) was demonstrated in heavily pretreated patients, although only five WT GIST patients were recruited in this phase II study [55]. In studies using imatinib in the adjuvant setting, subanalyses of WT GISTs in both the ACOSOG Z9001 trial (32 patients) [56] and the SSGXVIII (19 patients) [57] did not detect any benefit.

A recent report from the NIH Pediatric and Wildtype GIST Clinic demonstrated that the vast majority of the patients gained no clinical benefit from imatinib; only one out of 49 patients treated with imatinib mesylate had partial remission [4]. On the other hand, in the same study, seven out of 38 patients with SDH-deficient GISTs showed responses to sunitinib (one complete, three partial, three mixed). Our multicentre series of paediatric/young adult patients with advanced KIT/PDGFRA WT GISTs confirmed some clinical benefits of sunitinib (strong antiangiogenic inhibitor) in this population [58]. These data were similar to a series of Janeway et al. in paediatric GIST patients, in which longer time to progression on sunitinib as compared to prior imatinib therapy was observed [59]. Similarly, Murray noticed that sunitinib therapy had better outcomes in this type of GIST than imatinib. In a single institution study on SDH-deficient GIST, Liu et al. [18] reported four patients with disease progression during imatinib treat-

ment after initial resection, who all achieved disease control after changing therapy to sunitinib. It is suggested that the absence of functional SDH complex drives increased the vascular endothelial growth factor receptor (VEGFR) and insulin growth factor receptor (IGF1R) signalling *via* hypoxia-inducible factor HIF1-α transcriptional activity. This mechanism may be related to the efficacy of sunitinib, which inhibits both VEGFR and IGF1R, targeting these receptors and HIF2α, or their downstream effectors, making rationale for the use of antiangiogenic drugs. In another study, six patients with SDH-deficient GIST experienced clinical benefit from regorafenib, with tumour response (33.3%) or stable disease for at least 16 weeks [60]. This study, reported by Ben-Ami and co-workers, found potential improvement of PFS with regorafenib in patients with unresectable SDH-deficient GIST after failure of prior therapy with a tyrosine kinase inhibitor.

Overexpression of insulin-like growth factor receptor type 1 (IGFR1) at the protein level has also been observed in the majority of SDH deficient GISTs, with the exact molecular mechanism remaining unknown [16, 61, 62]. Since WT GIST frequently overexpress IGF1R, the SARC 022 phase II trial tested a new kinase inhibitor, linsitinib, with properties of potent inhibition of IGF1R [63]. Unfortunately, preliminary findings were not promising, with no objective response observed. PFS at 9 months was only 52%. Succinate dehydrogenase deficiency is related to hypermethylation of the genes involved in chromatin cell differentiation, thus the use of DNA hypomethylating agents is under investigation for these tumours [64]. There is currently a recruiting phase II clinical trial with the use of a new-generation DNA methyltransferase inhibitor, guadecitabine (SGI-110), in non-KIT/PDGFRA-mutated GIST and SDH-deficient paragangliomas and pheochromocytomas (NCT03165721). There are also other clinical trials operating specifically for SDH-deficient tumours, one using the glutaminase inhibitor CB-839 (NCT02071862) and one using a new-generation DNA methyltransferase inhibitor [65]. These trials are ongoing, and the results have not been yet disclosed. The hypermethylation status correlates with aberrant expression of FGF4, disrupting the binding of CTCF at DNA regions located on the boundaries of the FGF3/FGF4 locus; it was also recently discovered that FGFR1/FGFR2 receptors, and FGF4, FGF2, FGF7, and FGF10 ligands are highly expressed in SDH-deficient GIST [66, 67]. These may lead to novel potential treatment strategies using selective FGF/FGFR inhibitors, which is being currently tested in the frame of a clinical trial (NCT04595747).

Taking into account the biological features of SDH-deficient GIST, the new therapies of potential interest comprise PI3K/AKT/mTOR inhibitors, heat-shock protein inhibitors, HIF1-α targeting agents, epigenetic modifiers and demethylating agents. However, further researches are necessary in this fields.

The next possible target is related to the fact that SDH-deficient GIST typically feature widespread DNA methylation [68]. The actual occurrence of MGMT methylation in these tumours potentially predispose them to respond to alkylating drugs [69]. Recent and very interesting molecular data indicate that O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is markedly prevalent in SDH-deficient GIST, suggesting sensitivity to alkylating agents. One of the examples is temozolomide, an alkylating agent, which is ineffective in unselected GIST patient populations [70–72]. However, the study on 15 patients with paraganglioma and pheochromocytoma showed that 50% of SDHB-mutated patients had a partial response to temozolomide [73], while none of the SDHB wildtype patients had partial responses. These data suggest that SDHB mutations may be a kind of biomarker for sensitivity to temozolomide in paraganglioma and pheochromocytoma, which share genomic mutations and inheritance patterns to SDH-deficient GIST. Similarly, the report of Yebra et al., presented during the 2019 Annual Meeting of the Connective Tissue Oncology Society, demonstrated therapeutic vulnerability of SDH-deficient GISTs to temozolomide, with a 40% rate of objective responses among five patients treated with this drug [70]. Phase II study (NCT03556384) is ongoing [74]. Further preclinical and clinical research on SDH-deficient GISTs is needed.

Conclusions

To summarize the possible options of systemic therapy in SDH-deficient GIST, they have a high rate of primary resistance to various TKI. That said, even though related often to the indolent course of the disease, these tumours demonstrate some responsiveness to regorafenib and sunitinib. Further research with agents directed against other possible targets in SDH-deficient GIST are necessary.

Conflict of interest: none declared

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