Nowotwory rzadkie w onkologii /
Rare neoplasms in oncology

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 onco- genic *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 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 Reckling-ghausen disease) [9, 10], but also includes rare tumours that
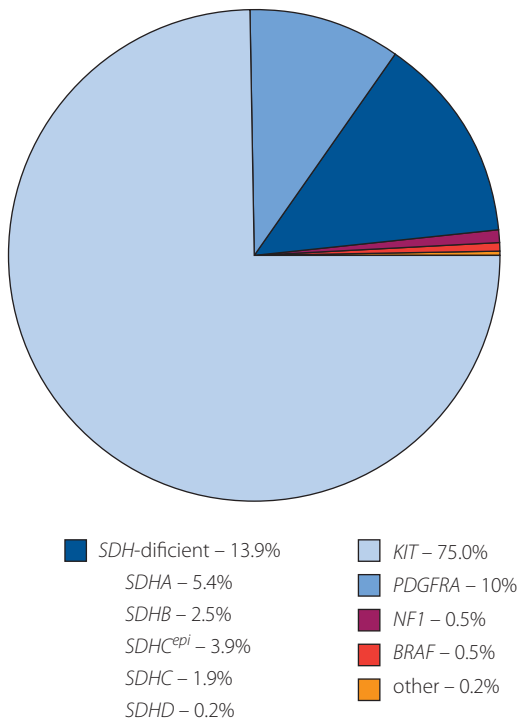
Figure 1. Molecular subtypes in GIST. Based upon Schaefer et al. [6]

Legend for pie chart:
- *SDH*-dificient – 13.9%
  - *SDHA* – 5.4%
  - *SDHB* – 2.5%
  - *SDHC^epi* – 3.9%
  - *SDHC* – 1.9%
  - *SDHD* – 0.2%
- *KIT* – 75.0%
- *PDGFRA* – 10%
- *NF1* – 0.5%
- *BRAF* – 0.5%
- other – 0.2%

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, 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].

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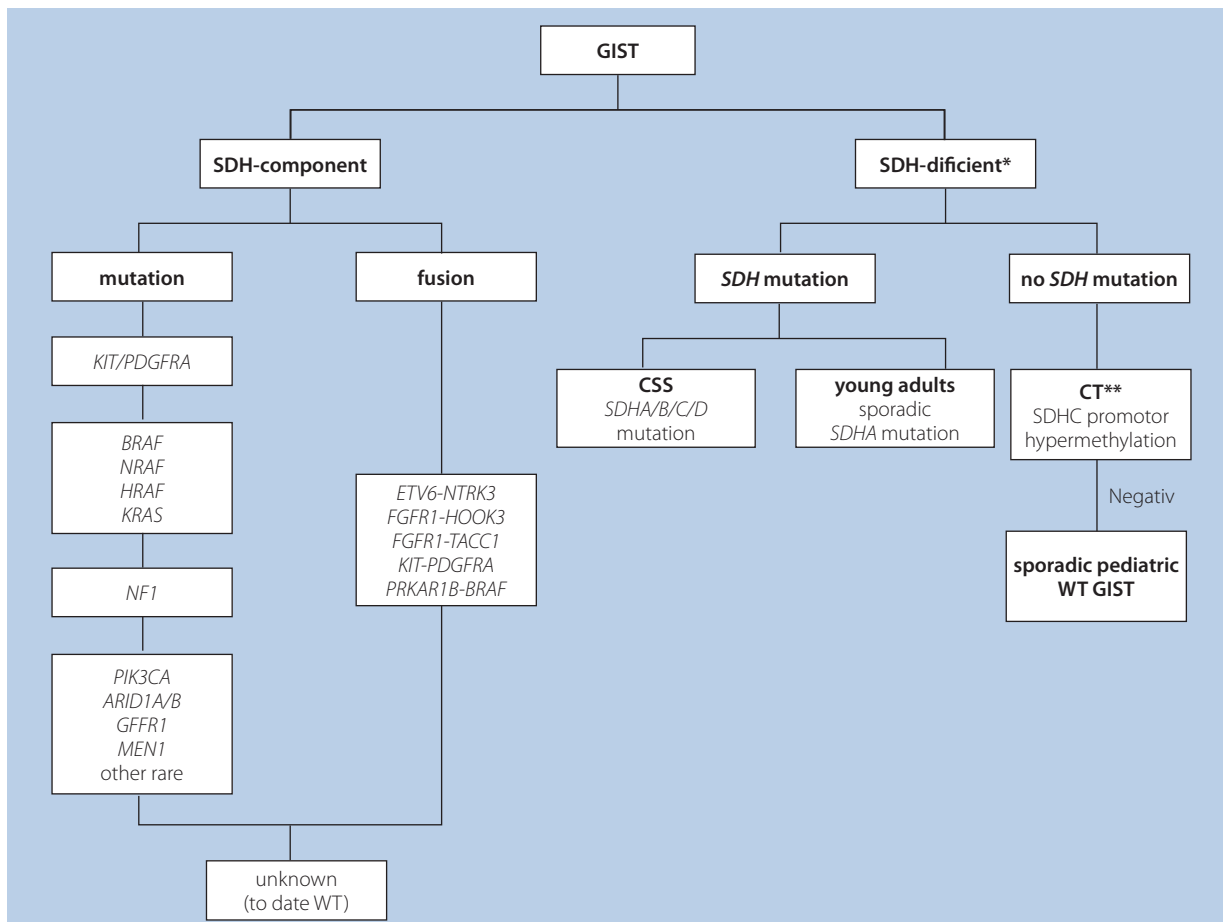
Figure 2. SDH-component and SDH-deficient sub-classification of GISTs [4, 9]

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].

Carney-Stratakis syndrome (CSS) is characterized by gastric multifocal GISTs and paragangliomas [19], showing an autosomal dominant inheritance pattern with incomplete

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

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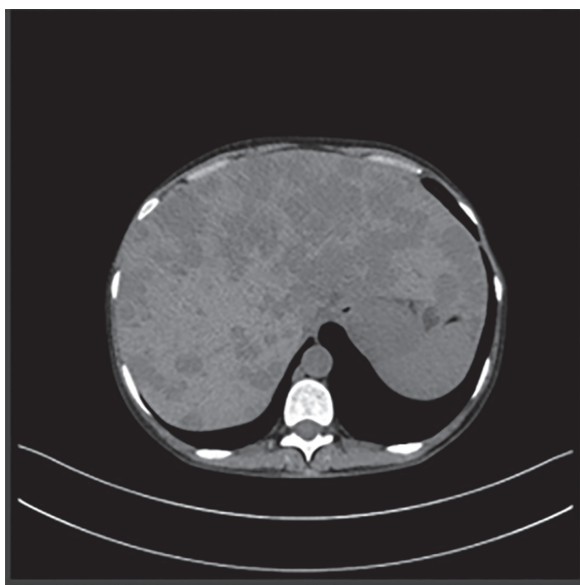

Figure 3. Computed tomography imaging demonstrating SDH-deficient gastric GIST with extensive liver metastases

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 from both truncating and missense germline mutations. *SDHA*-mutation associated GISTs occur at an older age than

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

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 re-

sponse 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 treatment after initial resection, who all achieved disease control after changing therapy to sunitinib. It is suggested that the absence of func-

tional 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* wild-type 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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References

1. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011; 11(12): 865–878, doi: 10.1038/nrc3143, indexed in Pubmed: 22089421.
2. Rutkowski P, Przybył J, Wozniak A, et al. Targeted Therapy in Gastrointestinal Stromal Tumors. Current Clinical Pathology. 2015: 163–196, doi: 10.1007/978-1-4939-2047-1_14.
3. Blay JY, Kang YK, Nishida T, et al. Gastrointestinal stromal tumours. Nat Rev Dis Primers. 2021; 7(1): 22, doi: 10.1038/s41572-021-00254-5, indexed in Pubmed: 33737510.
4. Boikos SA, Pappo AS, Killian JK, et al. Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol. 2016; 2(7): 922–928, doi: 10.1001/jamaoncol.2016.0256, indexed in Pubmed: 27011036.
5. Janeway KA, Kim SuY, Lodish M, et al. NIH Pediatric and Wild-Type GIST Clinic. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S

A. 2011; 108(1): 314–318, doi: 10.1073/pnas.1009199108, indexed in Pubmed: 21173220.

6. Schaefer IM, Mariño-Enríquez A, Fletcher JA. What is New in Gastrointestinal Stromal Tumor? Adv Anat Pathol. 2017; 24(5): 259–267, doi: 10.1097/PAP.0000000000000158, indexed in Pubmed: 28632504.

7. Wang JH, Lasota J, Miettinen M. Succinate Dehydrogenase Subunit B (SDHB) Is Expressed in Neurofibromatosis 1-Associated Gastrointestinal Stromal Tumors (Gists): Implications for the SDHB Expression Based Classification of Gists. J Cancer. 2011; 2: 90–93, doi: 10.7150/jca.2.90, indexed in Pubmed: 21479127.

8. Ibrahim A, Chopra S. Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumors. Arch Pathol Lab Med. 2020; 144(5): 655–660, doi: 10.5858/arpa.2018-0370-RS, indexed in Pubmed: 31169996.

9. Brčić I, Argyropoulos A, Liegl-Atzwanger B. Update on Molecular Genetics of Gastrointestinal Stromal Tumors. Diagnostics (Basel). 2021; 11(2), doi: 10.3390/diagnostics11020194, indexed in Pubmed: 33525726.

10. Maertens O, Prenen H, Debiec-Rychter M, et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. Hum Mol Genet. 2006; 15(6): 1015–1023, doi: 10.1093/hmg/ddl016, indexed in Pubmed: 16461335.

11. Miettinen M, Fetsch JF, Sobin LH, et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006; 30(1): 90–96, doi: 10.1097/01.pas.0000176433.81079.bd, indexed in Pubmed: 16330947.

12. Hostein I, Faur N, Primois C, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol. 2010; 133(1): 141–148, doi: 10.1309/AJCPPCKGA2QGBJ1R, indexed in Pubmed: 20023270.

13. Shi E, Chmielecki J, Tang CM, et al. FGFR1 and NTRK3 actionable alterations in "Wild-Type" gastrointestinal stromal tumors. J Transl Med. 2016; 14(1): 339, doi: 10.1186/s12967-016-1075-6, indexed in Pubmed: 27974047.

14. Lasota J, Felisiak-Golabek A, Wasag B, et al. Frequency and clinicopathologic profile of PIK3CA mutant GISTs: molecular genetic study of 529 cases. Mod Pathol. 2016; 29(3): 275–282, doi: 10.1038/modpathol.2015.160, indexed in Pubmed: 26796526.

15. Klug LR, Khosroyani HM, Kent JD, et al. New treatment strategies for advanced-stage gastrointestinal stromal tumours. Nat Rev Clin Oncol. 2022; 19(5): 328–341, doi: 10.1038/s41571-022-00606-4, indexed in Pubmed: 35217782.

16. Tarn C, Rink L, Merkel E, et al. Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. Proc Natl Acad Sci U S A. 2008; 105(24): 8387–8392, doi: 10.1073/pnas.0803383105, indexed in Pubmed: 18550829.

17. Miettinen M, Wang ZF, Sarlomo-Rikala M, et al. Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J Surg Pathol. 2011; 35(11): 1712–1721, doi: 10.1097/PAS.0b013e3182260752, indexed in Pubmed: 21997692.

18. Liu W, Zeng X, Wu X, et al. Clinicopathologic study of succinate-dehydrogenase-deficient gastrointestinal stromal tumors: A single-institutional experience in China. Medicine (Baltimore). 2017; 96(32): e7668, doi: 10.1097/MD.0000000000007668, indexed in Pubmed: 28796048.

19. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet. 2002; 108(2): 132–139, doi: 10.1002/ajmg.10235, indexed in Pubmed: 11857563.

20. Prakash S, Sarran L, Socci N, et al. Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. J Pediatr Hematol Oncol. 2005; 27(4): 179–187, doi: 10.1097/01.mph.0000157790.81329.47, indexed in Pubmed: 15838387.

21. Pantaleo MA, Lolli C, Nannini M, et al. Good survival outcome of metastatic SDH-deficient gastrointestinal stromal tumors harboring SDHA mutations. Genet Med. 2015; 17(5): 391–395, doi: 10.1038/gim.2014.115, indexed in Pubmed: 25188872.

22. Mason EF, Hornick JL. Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase-deficient Gastrointestinal Stromal Tumors: A Clinicopathologic Study of 76 Cases. Am J Surg Pathol. 2016; 40(12): 1616–1621, doi: 10.1097/PAS.0000000000000685, indexed in Pubmed: 27340750.

23. Gill AJ. Succinate dehydrogenase (SDH)-deficient neoplasia. Histopathology. 2018; 72(1): 106–116, doi: 10.1111/his.13277, indexed in Pubmed: 29239034.

24. Pitsava G, Settas N, Faucz FR, et al. Carney Triad, Carney-Stratakis Syndrome, 3PAS and Other Tumors Due to SDH Deficiency. Front Endocrinol (Lausanne). 2021; 12: 680609, doi: 10.3389/fendo.2021.680609, indexed in Pubmed: 34012423.

25. Sun F, Huo X, Zhai Y, et al. Crystal structure of mitochondrial respiratory membrane protein complex II. Cell. 2005; 121(7): 1043–1057, doi: 10.1016/j.cell.2005.05.025, indexed in Pubmed: 15989954.

26. Huang S, Millar AH. Succinate dehydrogenase: the complex roles of a simple enzyme. Curr Opin Plant Biol. 2013; 16(3): 344–349, doi: 10.1016/j.pbi.2013.02.007, indexed in Pubmed: 23453781.

27. Haller F, Moskalev EA, Faucz FR, et al. Aberrant DNA hypermethylation of SDHC: a novel mechanism of tumor development in Carney triad. Endocr Relat Cancer. 2014; 21(4): 567–577, doi: 10.1530/ERC-14-0254, indexed in Pubmed: 24859990.

28. Killian JK, Kim SuY, Miettinen M, et al. Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor. Cancer Discov. 2013; 3(6): 648–657, doi: 10.1158/2159-8290.CD-13-0092, indexed in Pubmed: 23550148.

29. Settas N, Faucz FR, Stratakis CA. Succinate dehydrogenase (SDH) deficiency, Carney triad and the epigenome. Mol Cell Endocrinol. 2018; 469: 107–111, doi: 10.1016/j.mce.2017.07.018, indexed in Pubmed: 28739378.

30. Gill AJ. Succinate dehydrogenase (SDH) and mitochondrial driven neoplasia. Pathology. 2012; 44(4): 285–292, doi: 10.1097/PAT.0b013e3283539932, indexed in Pubmed: 22544211.

31. Yebra M, Bhargava S, Kumar A, et al. Establishment of Patient-Derived Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumor Models for Predicting Therapeutic Response. Clin Cancer Res. 2022; 28(1): 187–200, doi: 10.1158/1078-0432.CCR-21-2092, indexed in Pubmed: 34426440.

32. Belinsky MG, Rink L, von Mehren M. Succinate dehydrogenase deficiency in pediatric and adult gastrointestinal stromal tumors. Front Oncol. 2013; 3: 117, doi: 10.3389/fonc.2013.00117, indexed in Pubmed: 23730622.

33. Miettinen M, Killian JK, Wang ZF, et al. Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in gastrointestinal stromal tumors (GISTs) signals SDHA germline mutation. Am J Surg Pathol. 2013; 37(2): 234–240, doi: 10.1097/PAS.0b013e3182671178, indexed in Pubmed: 23282968.

34. Miettinen M, Lasota J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs) - a review. Int J Biochem Cell Biol. 2014; 53: 514–519, doi: 10.1016/j.biocel.2014.05.033, indexed in Pubmed: 24886695.

35. Lv BB, Li JM, Yao ZG, et al. Succinate dehydrogenase deficient gastrointestinal stromal tumor in a three month old boy with a fatal clinical course: a case report and review of literature. Diagn Pathol. 2021; 16(1): 14, doi: 10.1186/s13000-021-01077-4, indexed in Pubmed: 33612108.

36. MacFarlane J, Seong KC, Bisambar C, et al. A review of the tumour spectrum of germline succinate dehydrogenase gene mutations: Beyond phaeochromocytoma and paraganglioma. Clin Endocrinol (Oxf). 2020; 93(5): 528–538, doi: 10.1111/cen.14289, indexed in Pubmed: 32686200.

37. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006; 23(2): 70–83, doi: 10.1053/j.semdp.2006.09.001, indexed in Pubmed: 17193820.

38. Pantaleo MA, Astolfi A, Indio V, et al. SDHA loss-of-function mutations in KIT-PDGFRA wild-type gastrointestinal stromal tumors identified by massively parallel sequencing. J Natl Cancer Inst. 2011; 103(12): 983–987, doi: 10.1093/jnci/djr130, indexed in Pubmed: 21505157.

39. Pantaleo MA, Astolfi A, Urbini M, et al. GIST Study Group. Analysis of all subunits, SDHA, SDHB, SDHC, SDHD, of the succinate dehydrogenase complex in KIT/PDGFRA wild-type GIST. Eur J Hum Genet. 2014; 22(1): 32–39, doi: 10.1038/ejhg.2013.80, indexed in Pubmed: 23612575.

40. Nannini M, Rizzo A, Indio V, et al. Targeted therapy in deficient GIST. Ther Adv Med Oncol. 2021; 13: 17588359211023278, doi: 10.1177/17588359211023278, indexed in Pubmed: 34262616.

41. Pantaleo MA, Urbini M, Schipani A, et al. Germline Variants in Adult Patients With -Mutant Gastrointestinal Stromal Tumor. Front Oncol. 2021; 11: 778461, doi: 10.3389/fonc.2021.778461, indexed in Pubmed: 35059314.

42. Wagner AJ, Remillard SP, Zhang YX, et al. Loss of expression of SDHA predicts SDHA mutations in gastrointestinal stromal tumors. Mod Pathol. 2013; 26(2): 289–294, doi: 10.1038/modpathol.2012.153, indexed in Pubmed: 22955521.

43. Casey RT, Ten Hoopen R, Ochoa E, et al. SDHC epi-mutation testing in gastrointestinal stromal tumours and related tumours in clinical practice. Sci Rep. 2019; 9(1): 10244, doi: 10.1038/s41598-019-46124-9, indexed in Pubmed: 31308404.

44. Weldon CB, Madenci AL, Boikos SA, et al. Surgical Management of Wild-Type Gastrointestinal Stromal Tumors: A Report From the National

Institutes of Health Pediatric and Wildtype GIST Clinic. J Clin Oncol. 2017; 35(5): 523–528, doi: 10.1200/JCO.2016.68.6733, indexed in Pubmed: 28029307.

45. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) Gastrointestinal Stromal Tumors (GISTs) Version 1.2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1507 (01.08.2022).

46. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002; 347(7): 472–480, doi: 10.1056/NEJMoa020461, indexed in Pubmed: 12181401.

47. Rutkowski P, Ziętek M, Cybulska-Stopa B, et al. The analysis of 3-year adjuvant therapy with imatinib in patients with high-risk molecular profiled gastrointestinal stromal tumors (GIST) treated in routine practice. Eur J Surg Oncol. 2021; 47(5): 1191–1195, doi: 10.1016/j.ejso.2020.08.004, indexed in Pubmed: 32826113.

48. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer. 2015; 121(9): 1405–1413, doi: 10.1002/cncr.29220, indexed in Pubmed: 25641662.

49. Demetri G, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381(9863): 295–302, doi: 10.1016/s0140-6736(12)61857-1.

50. Blay JY, Serrano C, Heinrich M, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020; 21(7): 923–934, doi: 10.1016/s1470-2045(20)30168-6.

51. Murray M, Hatcher H, Jessop F, et al. Treatment of wild-type gastrointestinal stromal tumor (WT-GIST) with imatinib and sunitinib. Pediatr Blood Cancer. 2008; 50(2): 386–388, doi: 10.1002/pbc.21312, indexed in Pubmed: 17729245.

52. Neppala P, Banerjee S, Fanta PT, et al. Current management of succinate dehydrogenase-deficient gastrointestinal stromal tumors. Cancer Metastasis Rev. 2019; 38(3): 525–535, doi: 10.1007/s10555-019-09818-0, indexed in Pubmed: 31773431.

53. Mei L, Smith SC, Faber AC, et al. Gastrointestinal Stromal Tumors: The GIST of Precision Medicine. Trends Cancer. 2018; 4(1): 74–91, doi: 10.1016/j.trecan.2017.11.006, indexed in Pubmed: 29413424.

54. Debiec-Rychter M, Sciot R, Le Cesne A, et al. EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, Australasian GastroIntestinal Trials Group. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer. 2006; 42(8): 1093–1103, doi: 10.1016/j.ejca.2006.01.030, indexed in Pubmed: 16624552.

55. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol. 2014; 25(1): 236–240, doi: 10.1093/annonc/mdt484, indexed in Pubmed: 24356634.

56. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol. 2014; 32(15): 1563–1570, doi: 10.1200/JCO.2013.51.2046, indexed in Pubmed: 24638003.

57. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. J Clin Oncol. 2016; 34(3): 244–250, doi: 10.1200/JCO.2015.62.9170, indexed in Pubmed: 26527782.

58. Rutkowski P, Magnan H, Chou AJ, et al. Treatment of gastrointestinal stromal tumours in paediatric and young adult patients with sunitinib: a multicentre case series. BMC Cancer. 2017; 17(1): 717, doi: 10.1186/s12885-017-3727-1, indexed in Pubmed: 29110655.

59. Janeway KA, Albritton KH, Van Den Abbeele AD, et al. Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. Pediatr Blood Cancer. 2009; 52(7): 767–771, doi: 10.1002/pbc.21909, indexed in Pubmed: 19326424.

60. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol. 2016; 27(9): 1794–1799, doi: 10.1093/annonc/mdw228, indexed in Pubmed: 27371698.

61. Janeway KA, Zhu MJ, Barretina J, et al. Strong expression of IGF1R in pediatric gastrointestinal stromal tumors without IGF1R genomic amplification. Int J Cancer. 2010; 127(11): 2718–2722, doi: 10.1002/ijc.25247, indexed in Pubmed: 20162573.

62. Mahadevan D, Sutton GR, Arteta-Bulos R, et al. Phase 1b study of safety, tolerability and efficacy of R1507, a monoclonal antibody to IGF-1R in combination with multiple standard oncology regimens in patients with advanced solid malignancies. Cancer Chemother Pharmacol. 2014; 73(3): 467–473, doi: 10.1007/s00280-013-2372-x, indexed in Pubmed: 24390424.

63. Mehren Mv, George S, Heinrich M, et al. Results of SARC 022, a phase II multicenter study of linsitinib in pediatric and adult wild-type (WT) gastrointestinal stromal tumors (GIST). J Clin Oncol. 2014; 32(15_suppl): 10507–10507, doi: 10.1200/jco.2014.32.15_suppl.10507.

64. Flavahan WA, Drier Y, Johnstone SE, et al. Altered chromosomal topology drives oncogenic programs in SDH-deficient GISTs. Nature. 2019; 575(7781): 229–233, doi: 10.1038/s41586-019-1668-3, indexed in Pubmed: 31666694.

65. Ricci R, Martini M, Ravegnini G, et al. Preferential MGMT methylation could predispose a subset of KIT/PDGFRA-WT GISTs, including SDH-deficient ones, to respond to alkylating agents. Clin Epigenetics. 2019; 11(1): 2, doi: 10.1186/s13148-018-0594-9, indexed in Pubmed: 30616628.

66. Indio V, Schipani A, Nannini M, et al. Gene Expression Landscape of SDH-Deficient Gastrointestinal Stromal Tumors. J Clin Med. 2021; 10(5), doi: 10.3390/jcm10051057, indexed in Pubmed: 33806389.

67. Astolfi A, Pantaleo MA, Indio V, et al. The Emerging Role of the FGF/FGFR Pathway in Gastrointestinal Stromal Tumor. Int J Mol Sci. 2020; 21(9), doi: 10.3390/ijms21093313, indexed in Pubmed: 32392832.

68. Lou L, Zhang W, Li J, et al. Abnormal MGMT Promoter Methylation in Gastrointestinal Stromal Tumors: Genetic Susceptibility and Association with Clinical Outcome. Cancer Manag Res. 2020; 12: 9941–9952, doi: 10.2147/CMAR.S269388, indexed in Pubmed: 33116851.

69. Ravegnini G, Ricci R. Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumors: Small Steps Toward Personalized Medicine? Epigenet Insights. 2019; 12: 2516865719842534, doi: 10.1177/2516865719842534, indexed in Pubmed: 31020269.

70. Yebra M, Bhargava S, Kumar A, et al. Human succinate dehydrogenase-deficient gastrointestinal stromal tumors are seinsitive to temozolomide via induction of ER stress and DNA damage: 10. https://www.ctos.org/Portals/0/PDF/2020%20CTOS%20Prelim%20Program_FINAL.pdf (01.08.2022).

71. Trent JC, Beach J, Burgess MA, et al. A two-arm phase II study of temozolomide in patients with advanced gastrointestinal stromal tumors and other soft tissue sarcomas. Cancer. 2003; 98(12): 2693–2699, doi: 10.1002/cncr.11875, indexed in Pubmed: 14669291.

72. Garcia del Muro X, Lopez-Pousa A, Martin J, et al. Spanish Group for Research on Sarcomas. A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas. Cancer. 2005; 104(8): 1706–1712, doi: 10.1002/cncr.21384, indexed in Pubmed: 16134177.

73. Hadoux J, Favier J, Scoazec JY, et al. SDHB mutations are associated with response to temozolomide in patients with metastatic pheochromocytoma or paraganglioma. Int J Cancer. 2014; 135(11): 2711–2720, doi: 10.1002/ijc.28913, indexed in Pubmed: 24752622.

74. Glod J, Arnaldez FI, Wiener L, et al. A Phase II Trial of Vandetanib in Children and Adults with Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumor. Clin Cancer Res. 2019; 25(21): 6302–6308, doi: 10.1158/1078-0432.CCR-19-0986, indexed in Pubmed: 31439578.

75. Dudzisz-Śledź M, Rutkowski P. Advances in the management of gastrointestinal stromal tumors (GISTs). Nowotwory. Journal of Oncology. 2020; 70(6): 280–287, doi: 10.5603/njo.2020.0055.