Editorial Commentary

Advances in therapy of succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumor

Piotr Rutkowski[1]^, Maria Debiec-Rychter[2]

[1]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [2]Department of Human Genetics, KU and University Hospitals Leuven, Leuven, Belgium

Correspondence to: Piotr Rutkowski, MD, PhD. Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Roentgena 5, 02-781 Warsaw, Poland. Email: piotr.rutkowski@pib-nio.pl.

Comment on: Nannini M, Rizzo A, Indio V, *et al.* Targeted therapy in SDH-deficient GIST. Ther Adv Med Oncol 2021;13:17588359211023278.

Received: 04 March 2022; Accepted: 09 May 2022; Published: 05 June 2022.

doi: 10.21037/gist-22-6

View this article at: https://dx.doi.org/10.21037/gist-22-6

Gastrointestinal stromal tumors (GISTs) comprise a heterogeneous group of the most common mesenchymal neoplasms of the gastrointestinal tract. The majority of GISTs are associated with activating, somatic, mutually exclusive mutations of two genes, *KIT* and *PDGFRA* (platelet-derived growth factor receptor-alpha), which are the early oncogenic events during GIST development (1). However, approximately 10–15% of GISTs lack oncogenic *KIT* or *PDGFRA* mutations and these tumors are often called "wild type" (WT) GISTs. They are indistinguishable from *KIT/PDGFRA*-mutated tumors in terms of morphology, anatomic localization and the expression of two diagnostic markers, i.e., KIT and DOG-1. Yet, they are a very heterogeneous group of tumors from the molecular point of view, which based on their succinate dehydrogenase (SDH) immunohistochemical status can be classified into two main subtypes, i.e., SDH-competent and SDH-deficient tumors. The former constitute mainly GIST related to neurofibromatosis type 1 (von Recklinghausen disease), but include also rare tumors that carry *BRAF* exon 15 mutations, oncogenic fusions of neurotrophic tyrosine kinase (*NTRK*), fusions or mutations in fibroblast growth factor receptor (*FGFR*) genes, and tumors of yet unknown driver mechanisms (2,3). In some of these WT cases (especially pediatric) overexpression of insulin-like growth factor 1 receptor (IGF1R) has been observed (4). The SDH-deficient GISTs form a distinctive subset of tumors, which results from the loss of function mutations in the genes encoding the SDH enzyme complex. These tumors comprise the majority of pediatric GISTs, low percentage of sporadic cases, and two classes of syndromic GISTs (Carney triad and Carney-Stratakis syndrome) (5-8). They are characterized by predominant location in the stomach, multifocality and often indolent clinical behavior even in metastatic disease

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 (9), and subsequently imatinib was applied in adjuvant therapy after resection of high-risk GIST (10). In case of GIST progression on imatinib therapy, the commonly used strategy is to introduce alternative molecular targeted agents as sunitinib, regorafenib and ripretinib (11-13).

KIT and *PDGFRA* mutational status strongly correlates with the response and progression-free survival (PFS) in GIST patients treated with imatinib. In general, patients with tumors harboring *KIT* exon 11 mutations demonstrate the best clinical response to imatinib with the highest rate of objective responses (70–85% of patients) and the longest overall and PFS (14,15). It has been observed that WT GIST had inferior response to imatinib and other tyrosine kinase inhibitors. Specifically, the SDH-deficient tumors are not well recognized in terms of sensitivity to tyrosine kinase inhibitors in large phase II and III clinical trials. Nevertheless, it seems that *SDH*-mutated GISTs

^ ORCID: 0000-0002-8920-5429.

do not respond well to the commonly used targeted therapy, with no objective tumor response to imatinib (16). Recently, Nannini and co-workers made a comprehensive review of targeted therapy in SDH-deficient GIST (17). Authors highlighted that disturbances in SDH complex lead to activation of hypoxia-inducible factor (HIF), what makes rationale for antiangiogenic drugs. They presented the overview of available data on the activity of different kinase inhibitors in this GIST subtype and confirmed low efficacy of these drugs, even beyond imatinib, especially in terms of objective responses. Authors underlined also that interpretation of disease stabilization in SDH-deficient GISTs is difficult in interpretation due to indolent course of disease. Nevertheless, our multicenter series of pediatric/young adult patients with advanced *KIT/PDGFRA* WT GISTs treated with sunitinib (strong antiangiogenic inhibitor), confirmed some clinical benefits of sunitinib in this population (18). These data were similar to series of Janeway *et al.* in pediatric GISTs patients, in which longer time to progression on sunitinib as compared to prior imatinib therapy was observed (19).

Very interesting molecular data indicate that O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is markedly prevalent in SDH-deficient GISTs, what may imply sensitivity to alkylating agents. With this regard, Nannini *et al.* did not mention in this review the results of preclinical and clinical data presented by Yebra *et al.* during 2019 Annual Meeting of Connective Tissue Oncology Society, which demonstrated therapeutic vulnerability of SDH-deficient GISTs to DNA alkylating agent, temozolomide, and 40% rate of objective responses among five patients treated with this drug (20,21). Phase II study (NCT03556384) is ongoing. Further preclinical and clinical research on SDH-deficient GISTs is needed.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gastrointestinal Stromal Tumor*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://gist.amegroups.com/article/view/10.21037/gist-22-6/coif). PR received payment or honoraria from BMS, MSD, Novartis, Pierre Fabre, Merck, Sanofi and he is on the Advisory Board of MSD, BMS, Merck, Sanofi, Pierre Fabre, Blueprint Medicines and Philogen. MDR has no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rutkowski P, Przybyl J, Wozniak A, et al. Targeted therapy in gastrointestinal stromal tumors. In: Russo A, Rosell R, Rolfo C. editors. Targeted therapy for solid tumors. New York: Springer Science, 2015.
2. Maertens O, Prenen H, Debiec-Rychter M, et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. Hum Mol Genet 2006;15:1015-23.
3. 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;2:922-8.
4. 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;105:8387-92.
5. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002;108:132-9.
6. 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;27:179-87.
7. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate

dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A 2011;108:314-8.
8. 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;2:90-3.
9. 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;347:472-80.
10. 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;47:1191-5.
11. 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;121:1405-13.
12. Demetri GD, 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;381:295-302.
13. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923-34.
14. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
15. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093-103.
16. Ibrahim A, Chopra S. Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumors. Arch Pathol Lab Med 2020;144:655-60.
17. Nannini M, Rizzo A, Indio V, et al. Targeted therapy in SDH-deficient GIST. Ther Adv Med Oncol 2021;13:17588359211023278.
18. 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;17:717.
19. 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;52:767-71.
20. Yebra M, Kumar A, Burgoyne A, et al. Paper #22: Human succinate dehydrogenase-deficient gastrointestinal stromal tumors are sensitive to temozolomide via induction of ER stress and DNA damage. 2020 CTOS Virtual Annual Meeting; November 18-21, 2020.
21. 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;28:187-200.

doi: 10.21037/gist-22-6
Cite this article as: Rutkowski P, Debiec-Rychter M. Advances in therapy of succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumor. Gastrointest Stromal Tumor 2022;5:5.