Metastatic and multiply relapsed SDH deficient GIST and paraganglioma displays clinical response to combined Poly ADP-Ribose Polymerase inhibition and Temozolomide

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Abstract

Pediatric GIST (gastrointestinal stromal tumors) are mostly KIT/ PDGFRA-WT and harbor mutations in SDH (succinate dehydrogenase), making them TKI (tyrosine kinase inhibitor) resistant due to the absence of gain-of-function tyrosine kinase mutations. Due to rarity of GIST in children, there have been few clinical trials available for patients with advanced disease, resulting in limited treatment options and a lack of pediatric-specific consensus guidelines. Here, we report the case of a patient with progressive, metastatic SDHB-mutant GIST that displayed a significant clinical response with a combination of Olaparib and TMZ (temozolomide).

Introduction

Unlike gastrointestinal stromal tumors (GISTs) in adults, the majority of GIST in pediatric patients do not harbor KIT/PDGFA mutations (WT-GIST)[1]. WT-GIST are further subclassified as succinate-dehydrogenase(SDH)-competent or SDH-deficient based on immunohistochemical staining for SDHB, with approximately 5 to 7.5% of GIST classified as SDH-negative[2]. In patients harboring germline SDH mutations, GIST frequently co-occur with paragangliomas, also known as Carney-Stratakis syndrome[3]. SDHB mutations in particular are associated with the development of tumors at an earlier age and with a higher propensity for malignant and metastatic disease[4-6].

Surgical resection is the mainstay of treatment for localized GIST. For advanced stage GIST with mutations in KIT and PDFGRA, tyrosine kinase inhibitors such as imatinib and sunitinib have prolonged progression free survival (PFS), but compete response is rare, and patients can develop either primary (10-15%) or late resistance[7,8]. Conversly, WT-GIST are resistant to imatinib and other TKIs resulting in few available treatment options for metastatic disease[9,10].

Here, we report the case of a patient with progressive, metastatic SDHB-mutant GIST that displayed a significant clinical response with a combination of Olaparib and TMZ.

Case presentation

Patient is an African American female that presented as a 13-year-old with refractory anemia. Endoscopy showed multiple gastric submucosal masses with superficial ulceration. A CT-scan showed a 2.5 x 2.6 cm mass in the fundus of the stomach and a precarinal 2.6-mm lymph node in the chest. She underwent partial gastrectomy and pathology was consistent with multifocal GIST. Postoperatively, she was started on imatinib 400 mg daily. Two years after surgical resection, a new FDG avid hypodensity was detected in the left lobe of the liver. Imatinib dose was increased to 600 mg daily but a PET scan 3 months later revealed several new FDG avid foci in the liver. Patient was transitioned to sunitinib 50 mg daily but developed a rash, hypothyroidism and myelosuppression requiring cessation of treatment.

At this time, a CT-scan showed a mediastinal lesion, measuring 4.5 x 5.3 cm as well as a roughly 2-cm gastric junction lesion. There were no focal liver lesions appreciated. The mediastinal lesion was favored to be a paraganglioma and an MIBG scan confirmed positive uptake, suggestive of Carney Stratakis syndrome. The patient then underwent focused genetic testing of her GIST tumor and this did not reveal any somatic mutations in KIT or PDGFRA.

Patient was off all therapy for 2 years and CT scans continued to show gradual increased size of the gastroesophageal lesion to 2.4 cm and increased size of the liver lesions, the largest being 2.2 cm. The patient was started on Nilotinib at 200 mg twice daily but this was stopped within a week due to intolerable side effects. She was then restarted on sunitinib 25 mg daily for four weeks on and two weeks off. Repeat scans continued to show increasing size of multiple enhancing liver lesions and she underwent hepatic embolization with doxorubicin. Post embolization, a partial response was seen with some hepatic metastases reduced in size and/or having reduced enhancement.

Additional tumor profiling was sent using the Oncomine panel and this failed to detect any somatic variants. Additionally, PDL1 expression was not detected, and the tumor was microsatellite stable. She remained on sunitinib, but given the lack of targetable mutations, she was enrolled on a Phase II study of heat shock protein inhibitor AUY922 at a dose 70mg/m2. She was treated with 6 cycles but repeat imaging showed progression of liver lesions and she was taken off study. Patient was then enrolled on a phase II trial of Vandetinib 200mg daily but experienced significant toxicity requiring multiple interruptions and she ultimately came off study after 8 months.

After discontinuation of vandetinib, a PET scan showed interval increase in hypermetabolic lesions in the region of the stomach and interval increase in numerous hypermetabolic hepatic lesions. She was started on Regorafenib 160 mg x 21 days on, 7 days off. However, this was stopped due to severe hypertension, dermatologic toxicities, nephrotoxicity and hepatotoxicity.

While off therapy, a repeat CT-scan showed increased size of the mediastinal paraganglioma that had been present since diagnosis. She underwent sternotomy and resection of the middle mediastinal tumor requiring cardiopulmonary bypass and reconstruction of the pulmonary artery along with thymectomy.

The patient was then monitored off all medications for 4 years but began experiencing severe back pain. A PET scan showed increase burden of liver metastatic disease and new multifocal osseous metastases and a new small left anterior mediastinal lesion. An MIBG was performed and none of the FDG avid metastases displayed any MIBG uptake.

At this point, the patient's disease had not responded to multiple TKIs and two Phase I/II trials. Based on preliminary pre-clinical data from our laboratory showing synergistic activity of PARP inhibition and TMZ in an SDHB-mutant tumor model (unpublished), patient was started on olaparib 200 mg twice a day x 7 days + TMZ 75 mg/m^2/d x 7 days in 21-day cycles. After 6 cycles, a repeat PET showed markedly decreased hypermetabolism within osseous metastases with interval sclerosis and resolved hypermetabolic left anterior mediastinal mass. There was also slightly decreased hypermetabolic disease within the gastric primary tumor and hepatic metastases (Fig. 1&2).

Regarding side effects, patient endorsed severe nausea for which her TMZ dose was reduced in cycle 2 and anti-emetics were increased. In cycle 6, she received dexamethasone for chemotherapy induced nausea and developed severe steroid induced psychosis ultimately leading to a discontinuation of her chemotherapy for 8 months. A repeat PET scan after being off therapy showed progression of one hepatic metastases with decrease hypermetabolism in gastric and osseous metastases (Fig. 3). She restarted chemotherapy with Olaparib and TMZ and is tolerating it well.

Discussion and Conclusions

Surgical resection is the mainstay of treatment for localized GIST, but for advanced stage disease there are limited treatment options[11,12]. Unlike GIST in adults, most GIST in pediatric patients are KIT/ PDGFRA-WT and harbor mutations in SDH, making them resistant to TKIs[1,13]. Due in part to the rarity of GIST in

children, there have been few clinical trials available for pediatric patients further limiting treatment options and compounding the difficulty in managing patients with advanced disease[13,14].

While the role of cytotoxic therapy is limited in GIST, TMZ is an alkylating agent that has been used to treat select patients. A case report by D'Silva et al[15] described a patient with SDH-deficient GIST resistant to TKIs that was treated with TMZ at 150-200 mg/m^2 for 5 days, every 28 days. An FDG-PET scan after 4 cycles demonstrated stable disease and a CT scan after 7 cycles showed a partial response. A study of 15 patients with paraganglioma and pheochromocytoma showed that 50% of those with SDHB-mutations demonstrated a partial response to TMZ while no SDHB wild-type patients showed a response[16]. Yebra et al[17] established patient-derived SDH-mutant GIST models and found that TMZ elicits DNA damage and apoptosis in SDH- mutant cells. The authors applied their findings to a cohort of 5 patients with SDH-mutant GIST and found a 40% objective response rate and 100% disease control rate with TMZ at 85mg/m^{2}daily administered in 4-week cycles for 21 days. A Phase II clinical trial is currently underway to investigate the efficacy of TMZ in SDH-deficient GIST (ClinicalTrials.gov NCT03556384).

SDH is a key element of the Krebs cycle and loss of function can cause accumulation of the oncometabolite succinate, which has been shown to competitively inhibit αKG–dependent dioxygenases[18,19]. Previous work from our group has established that elevated levels of succinate leads to inhibition of lysine-specific demethylase 4B (KDM4B), resulting in aberrant hypermethylation of histone 3 lysine 9 (H3K9) at loci surrounding DNA breaks inhibiting recruitment of homologous recombination (HR) factors and rendering cells vulnerable to synthetic-lethal targeting with PARP inhibitors[20,21]. Recently, we have extended these findings to demonstrate additional synergistic combinations that exploit SDHB-induced HR defects. TMZ mediates cytotoxic effects by attaching methyl groups to DNA. The N3-MetA and N7-MetG adducts in particular are repaired via the base excision repair (BER) pathway in a process involving PARP, providing the basis for potential synergy. In a pre-clinical study, we demonstrated significant *in vitro*cytotoxicity and *in vivo* tumor growth delay in engineered SDHB-KO tumor models with combined treatment of TMZ and the PARP inhibitor BGB-290 (unpublished).

Here, we present a patient with metastatic, progressive SDH-deficient GIST, who's disease was refractory to multiple TKIs and failed multiple phase I/II trials. Using our pre-clinical findings as a rationale, we treated the patient with a combination of Olaparib and TMZ. After 6 cycles of treatment, the patient experienced significant clinical benefit with a partial response of disease. To our knowledge, this is the first report of a patient with SDH-deficient GIST treated with a combination of PARP inhibitor and TMZ.

The clinical response observed in this patient with progressive disease warrants consideration for further study in prospective clinical trials using a combination of PARP inhibition and TMZ for the treatment of SDH-deficient malignancies.

Conflict of Interest Statement: The authors have no conflicts of interest to disclose

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References

1. Janeway KA, Liegl B, Harlow A, et al. Pediatric KIT wild-type and platelet-derived growth factor receptor alpha-wild-type gastrointestinal stromal tumors share KIT activation but not mechanisms of genetic progression with adult gastrointestinal stromal tumors. *Cancer Res* . Oct 1 2007;67(19):9084-8. doi:10.1158/0008-5472.CAN-07-1938

2. Nannini M, Rizzo A, Indio V, Schipani A, Astolfi A, Pantaleo MA. Targeted therapy in SDH-deficient GIST. *Ther Adv Med Oncol* . 2021;13:17588359211023278. doi:10.1177/17588359211023278

3. Pitsava G, Settas N, Faucz FR, Stratakis CA. 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

4. Vanharanta S, Buchta M, McWhinney SR, et al. Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma. *Am J Hum Genet* . Jan 2004;74(1):153-9. doi:10.1086/381054

5. Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. *J Urol* . Dec 2012;188(6):2063-71. doi:10.1016/j.juro.2012.08.030

6. Boedeker CC, Neumann HP, Maier W, Bausch B, Schipper J, Ridder GJ. Malignant head and neck paragangliomas in SDHB mutation carriers.*Otolaryngol Head Neck Surg* . Jul 2007;137(1):126-9. doi:10.1016/j.otohns.2007.01.015

7. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* . Aug 15 2002;347(7):472-80. doi:10.1056/NEJMoa020461

8. Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. *J Clin Oncol* . Aug 20 2005;23(24):5795-804. doi:10.1200/JCO.2005.11.601

9. 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* . Jul 1 2016;2(7):922-8. doi:10.1001/jamaoncol.2016.0256

10. 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* . Nov 1 2019;25(21):6302-6308. doi:10.1158/1078-0432.CCR-19-0986

11. Mei L, Du W, Idowu M, von Mehren M, Boikos SA. Advances and Challenges on Management of Gastrointestinal Stromal Tumors. *Front Oncol* . 2018;8:135. doi:10.3389/fonc.2018.00135

12. Sicklick JK, Lopez NE. Optimizing surgical and imatinib therapy for the treatment of gastrointestinal stromal tumors. *J Gastrointest Surg* . Nov 2013;17(11):1997-2006. doi:10.1007/s11605-013-2243-0

13. Janeway KA, Pappo A. Treatment guidelines for gastrointestinal stromal tumors in children and young adults. *J Pediatr Hematol Oncol* . May 2012;34 Suppl 2:S69-72. doi:10.1097/MPH.0b013e31824e3899

14. Pappo AS, Janeway KA. Pediatric gastrointestinal stromal tumors.*Hematol Oncol Clin North Am* . Feb 2009;23(1):15-34, vii. doi:10.1016/j.hoc.2008.11.005

15. De Silva M, Rastogi S, Chan D, et al. Succinate dehydrogenase-deficient gastrointestinal stromal tumor: from diagnostic dilemma to novel personalised therapy in 2 case reports. *Transl Cancer Res* . Jul 2021;10(7):3588-3599. doi:10.21037/tcr-21-131

16. 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* . Dec 1 2014;135(11):2711-20. doi:10.1002/ijc.28913

17. 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* . Jan 1 2022;28(1):187-200. doi:10.1158/1078-0432.CCR-21-2092

18. Pollard PJ, Briere JJ, Alam NA, et al. Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. *Hum Mol Genet* . Aug 1 2005;14(15):2231-9. doi:10.1093/hmg/ddi227

19. Eijkelenkamp K, Osinga TE, Links TP, van der Horst-Schrivers ANA. Clinical implications of the oncometabolite succinate in SDHx-mutation carriers. *Clin Genet* . Jan 2020;97(1):39-53.

doi:10.1111/cge.13553

20. Sulkowski PL, Sundaram RK, Oeck S, et al. Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair. *Nat Genet* . Aug 2018;50(8):1086-1092. doi:10.1038/s41588-018-0170-4

21. Sulkowski PL, Oeck S, Dow J, et al. Oncometabolites suppress DNA repair by disrupting local chromatin signalling. *Nature* . Jun 2020;582(7813):586-591. doi:10.1038/s41586-020-2363-0

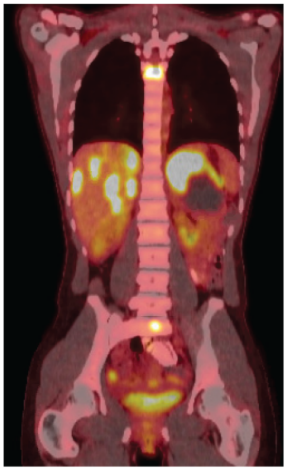
Figures Legends:

Figure 1. FDG-PET/CT prior to the start of Olaparib and Temozolomide.

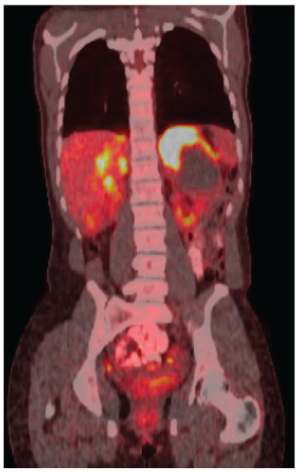
Figure 2. FDG-PET/CT after 6 cycles of Olaparib and Temozolomide.

Figure 3. FDG-PET/CT after 8 months off therapy.

Figure 1



Fgure 2



Fgure 3