Case Report

Fourth-line targeted drugs for the long-term treatment of patients with secondary gastrointestinal stromal tumors with multisite mutations: a case report

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Background: The surgical treatment of small intestinal stromal tumors is mainly based on the common experience of gastrointestinal stromal tumors (GISTs). The biological characteristics of tumors and secondary gene mutations during disease progression cause many difficulties in clinical treatment. Advanced GISTs usually have no chance to surgery especially after multiple lines of drug therapy and multiple surgeries. This case report provides a good example of rensformational surgery for advanced GIST.

Case Description: In this report, we describe the case of a patient that is male 57 years old with a small intestinal stromal tumor (stage IV) treated in our center (The First Medical Centre, Chinese PLA General Hospital, Beijing, China) who underwent more than 20 years of first- to fourth-line tyrosine kinase inhibitor (TKI) drug treatment and three rounds of surgical treatment. In June 2020, the patient developed extensive metastases in the abdominal cavity, pelvic cavity, and liver, and could not be treated surgically. The patient was enrolled in the "two-arm clinical trial of bridge therapy with ripretinib and sunitinib in China", started four cycles of ripretinib drug therapy and tumor evaluation, and eventually achieved tumor remission. The patient received surgical treatment following conversion therapy and postoperative tumor recurrence. After continued targeted therapy with TKIs, disease progression was controlled, and the patient's survival was prolonged.

Conclusions: Type II TKIs such as ripretinib and avapritinib have enhanced the typically expected therapeutic effects of many advanced GISTs. For the late-line treatment of advanced GIST, new TKI drugs can be tried for conversion therapy while monitoring the whole process, grasp the timing of surgery to provide more effective treatment.

Keywords: Gastrointestinal stromal tumors (GISTs); targeted therapy; long-term survival; case report

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Introduction

It is generally believed that the prognosis of small intestinal stromal tumors is poor, and there are currently few reports of these tumors (1-4). In 2006, Miettinen *et al.* (5) reported on the clinical, pathological, and molecular biological characteristics of 906 small intestinal stromal tumor cases; this study comprised a relatively large cohort, which facilitated the comprehensive investigation of small

intestinal stromal tumors. At present, the surgical treatment of small intestinal stromal tumors is still mainly based on the common experience of gastrointestinal stromal tumors (GISTs). The whole process of management during drug treatment for advanced GISTs is directly related to the prognosis of the disease. Choosing the right strategy at the right time for treatment can control the progression of the disease for a long time, and even make the disease remission. Advanced GISTs usually have no chance to surgery especially after multiple lines of drug therapy and multiple surgeries. This case report provides a good example of rensformational surgery for advanced GIST. We present the following article in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1361/rc).

Case presentation

A 57-year-old male patient sought treatment in April 1999 due to abdominal pain. A computed tomography (CT) examination revealed a "small intestinal tumor", and the patient underwent a "small intestinal tumor resection". A diagnosis of "small intestinal leiomyoma" was provided by the pathology report, and no treatment or regular review was performed after the operation. In December 2007, the patient developed abdominal pain symptoms that progressively worsened. In August 2008, an abdominal CT examination showed a "small intestinal stromal tumor with liver and pelvic metastasis". Recurrent abdominal tumor resection, liver metastasectomy, cholecystectomy, and pelvic tumor resection were performed concurrently. The postoperative pathological diagnosis was a (small intestine) moderately malignant stromal tumor involving the greater omentum (+), pelvic cavity (+), mesenteriolum (+), left and right lobes of the liver (+), bladder wall (+), and abdominal cavity (+), which exhibited the following characteristics: cluster of differentiation (CD) 117 (+), CD34 (+), S-100 (–), and smooth muscle antigen (SMA) (–). Oral imatinib mesylate was started 2 weeks after surgery according to the doctor's instructions. In December 2016, CT re-examination revealed abdominal space-occupying lesions. Considering the recurrence of abdominal GIST, the dose of imatinib mesylate was increased to 600 mg quaque die (QD). CT re-examination in February 2017 revealed disease progression.

The patient underwent CT-guided abdominal tumor biopsy and gene sequencing and was pathologically diagnosed with an (upper abdominal subcutaneous) spindle cell tumor. The immunohistochemistry results supported GIST and were as follows: PDGFR-a (+), Ki-67 (15%), CD34 (vascular +), CD117 (+), DOG-1 (+), and S-100 (–). The *C-KIT* gene mutation detection results were as follows: Exon 9: no mutation; Exon 11: deletion mutation (c.1669_1674delTGGAAG, p.Trp557_Lys558del); Exon 13: missense mutation (c.1961T>C; p.Val654Ala); and Exon 17: no mutations. The PDGFRA gene mutation detection results were as follows: Exon 12: no mutations; and Exon 18: no mutations.

Oral sunitinib malate was started in February 2017 with a dose of 37.5 mg. In April 2020, the patient's CT re-examination revealed recurrence and metastasis of the GIST in the abdominal cavity, liver, and pelvis. Disease recurrence and progression were considered, and the treatment was changed to oral regorafenib therapy. Severe gastrointestinal bleeding occurred, which was considered an adverse drug reaction, and the drug was discontinued. In May 2020, the patient was started on imatinib mesylate again. CT re-examination in June 2020 revealed that the tumor was not effectively controlled, and the disease had progressed. The diagnosis and treatment timeline are shown in *Figure 1*.

At this time, the patient's abdominal wall tumor was extending from the plane of the abdomen, exhibiting a protruding shape with a dark red surface and an area of approximately 8×8 cm. It had a medium texture on palpation and an unclear border. The intra-abdominal tumor border was not palpable. Shifting dullness was negative, and bowel sounds were heard 2–3 times/min. Laboratory examination showed mild anemia, with a hemoglobin level of 10^6 g/L and a red blood cell count of 3.54×10^{12}/L. Abdominal enhanced CT revealed multiple nodules in the abdominal peritoneum, i.e., omentum, as well as multiple nodules and mass shadows between the liver and stomach and between the spleen and stomach. The maximum diameter was

Highlight box

Key findings

- Type II TKIs have enhanced the typically expected therapeutic effects.

What is known and what is new?

- For the late-line treatment, new TKI drugs can be tried.
- Selecting the appropriate timing of surgical treatment is important.

What is the implication, and what should change now?

- New TKI drugs can be tried for conversion therapy.

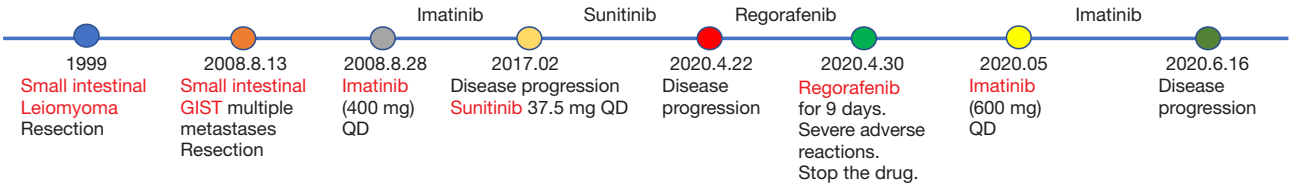

Figure 1 The patient's diagnosis and treatment timeline from 1999 to 2020. GIST, gastrointestinal stromal tumors; QD, quaque die.

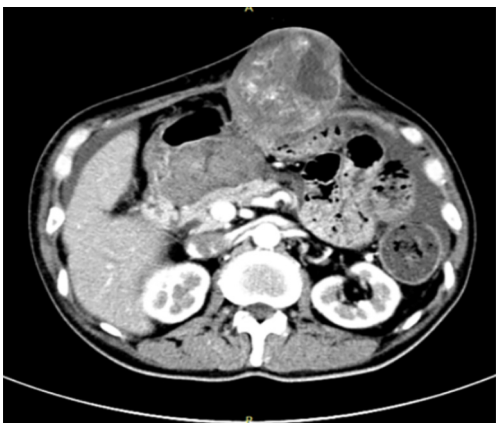

Figure 2 CT of abdominal wall metastases. CT, computed tomography.

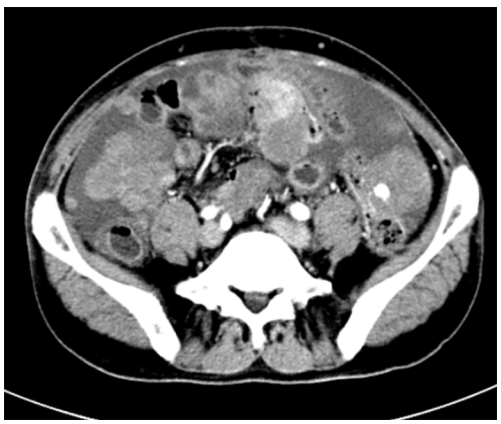

Figure 3 CT of abdominal and pelvic metastases. CT, computed tomography.

approximately 65 mm. A mass with an 82-mm maximum diameter in the anterior abdominal wall in front of the stomach body with poorly defined peripheral tissues and abnormal enhancement was also observed, and no obvious swollen lymph nodes were observed in the retroperitoneum. Abdominal wall tumors were considered to be GIST metastases (*Figures 2* and *3*).

In the analysis and discussion by the GIST multidisciplinary team (MDT) in the Chinese People's Liberation Army General Hospital, we considered that the patient had a long history of GIST and had undergone two surgeries and 1–3 lines of drug treatment. Therefore, radical surgery would be difficult. Effective disease control or conversion therapy that provides surgical opportunities to achieve a radical cure or tumor reduction and reduced tumor burden was determined to be the ideal treatment.

In August 2020, the patient was screened and enrolled in a clinical drug trial of ripretinib (a single-arm, open-label, multicenter phase II clinical trial to evaluate the efficacy, safety, and pharmacokinetic characteristics of DCC-2618 in patients with advanced GIST that progressed after treatment). Oral administration of ripretinib (150 mg QD) was started on August 13, 2020, and drug administration was terminated on December 18, 2020. The drug was administered for a total of 4 months. Five tumors with a tumor diameter greater than 30 mm on CT images were selected for a total of four modified Response Evaluation Criteria in Solid Tumors (mRECIST) evaluations (*Tables 1*,*2*, *Figure 4*). The CT images of the tumors after 4 months of ripretinib treatment showed that the overall CT values of the abdominal wall tumors were reduced due to liquefaction and necrosis, but the volume had increased, and the abdominal and pelvic tumors had regressed significantly. The overall evaluation was stable disease (SD) (*Figure 5*). The patient's abdominal wall tumor volume gradually increased, the skin became thinner, and ischemia and blackening occurred (*Figure 6*). Upon communicating with the patient and considering the risk of abdominal wall rupture and bleeding as well as the maximum benefit to the patient, we recommended surgical treatment of the abdominal wall and abdominal cavity tumors.

On December 22, 2020, the patient underwent abdominal wall tumor resection, resection of multiple abdominal pelvic tumors, partial colon resection, partial small intestine resection, partial gastrectomy, small intestine colostomy, and abdominal wall defect reconstruction. There

Table 1 Changes in tumor mRECIST assessment [longest diameter (mm)]

Tumor	Time				
	Baseline	After 1 month	After 2 months	After 3 months	After 4 months
Abdominal tumor 1	81.9	85.5	79.5	63.4	64.8
Abdominal wall mass 2	89.8	90.3	97.1	97.8	118.8
Abdominal tumor 3	70.8	71.5	83.6	72.9	62.6
Pelvic tumor 4	50.8	43.7	52.5	34.6	52.6
Pelvic tumor 5	32	34.8	33.5	14	14.2
Total diameter (mm)	325.3	325.8	346.2	282.7	313

mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Table 2 Ratio of the changes in the longest tumor diameter

Tumor	Time				
	Baseline	After 1 month	After 2 months	After 3 months	After 4 months
Abdominal tumor 1	1	104.4%	97.1%	77.4%	79.1%
Abdominal wall mass 2	1	100.6%	108.1%	108.9%	132.3%
Abdominal tumor 3	1	101.0%	118.1%	103.0%	88.4%
Pelvic tumor 4	1	86.0%	103.3%	68.1%	103.5%
Pelvic tumor 5	1	108.8%	104.7%	43.8%	44.4%
Total diameter change	1	100.2%	106.4%	86.9%	96.2%

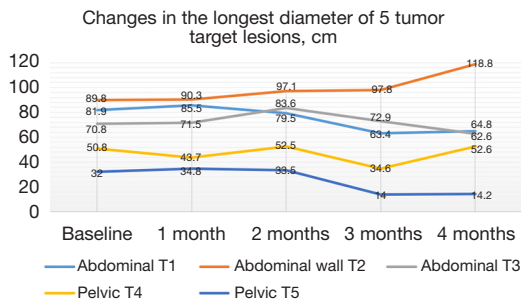

Figure 4 Changes in the longest diameter of the target lesions.

were nine tumors in the surgical specimen. The pathology of the nine tumors as seen by the naked eye was as follows:

(I) Abdominal wall mass + part of the colon: irregular tissue, approximately 18 cm × 17 cm × 14 cm, with skin attached to the surface, a skin area of 18 cm × 17 cm, a basal adhesion colon length of 12 cm, a circumference of 5–7 cm, a book-shaped incision, and a mass on the cut surface (17 cm × 16 cm × 14 cm). The section was gray and white, solid, and soft with a large amount of necrosis, and there was no adipose tissue around the intestine.

(II) Abdominal wall nodules: a group of gray and white nodules. The total size was approximately 8 cm × 8 cm × 4 cm, and the section was gray-white and gray-red, solid, with a hard texture.

(III) Mass at the lesser curvature of the stomach: one multinodular mass, 10 cm × 8 cm × 7 cm; the section was gray, solid, and soft.

(IV) Mesenteric nodules: more than 10 nodules with a diameter of 0.5–10 cm.

(V) Left diaphragmatic nodules: two nodules, 0.8–2 cm in diameter.

(VI) Pelvic floor nodule: one nodule, approximately 7 cm × 4 cm × 3.5 cm; the section was gray, white, and solid with a soft texture.

(VII) Rectal mass: the section of the intestinal tube was 15 cm long, with a circumference of 5–7 cm, and several gray nodules with a diameter of 0.5–8 cm were seen on the serosal surface of the intestinal tube. The section was gray and solid with a soft

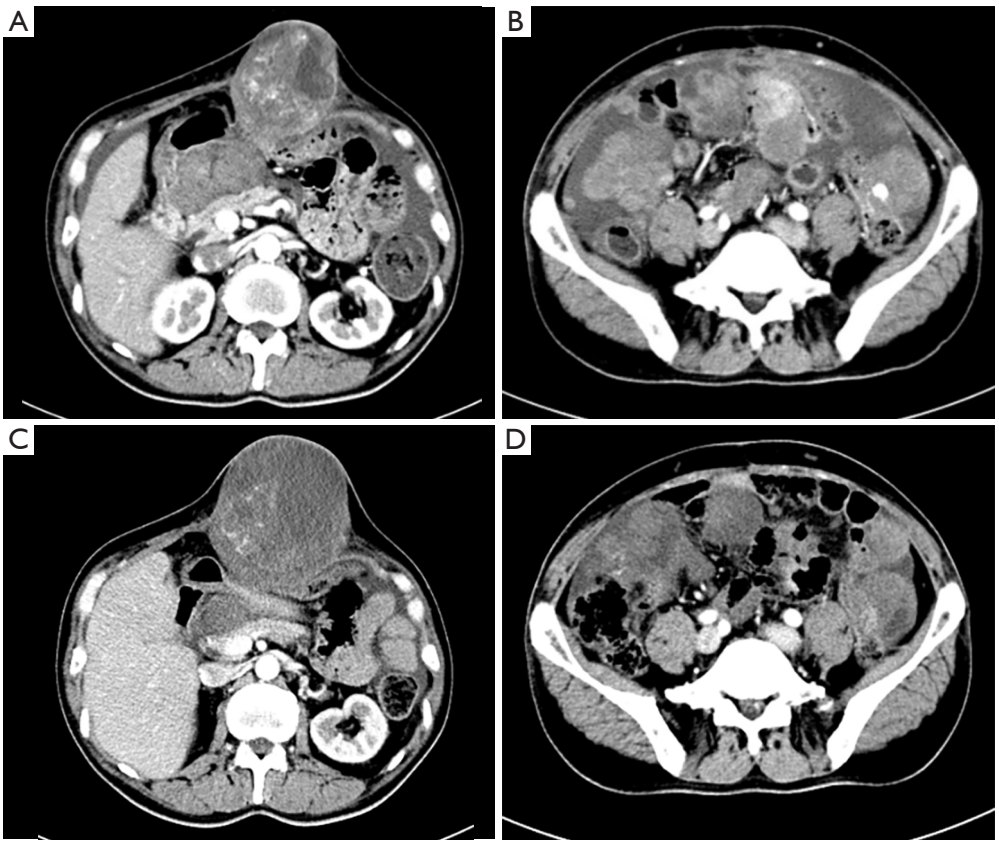

Figure 5 Comparison of baseline tumor CT images (A,C) and CT images of the tumor after 3 months of ripretinib administration (B,D). CT, computed tomography.

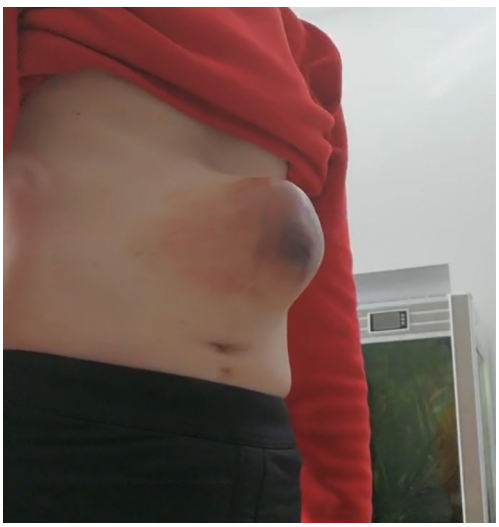

Figure 6 Photograph of the patient's abdominal wall tumor after treatment.

texture.

(VIII) Mass in the terminal ileum: the section of the intestinal tube was 27 cm long, with a circumference of 5–7 cm, and several nodules with a diameter of 1–5 cm were seen on the serosal surface of the intestinal tube. The section was gray and solid, with a soft texture.

(IX) Right diaphragmatic nodule: one nodule, 2.5 cm in diameter. The morphology, pathology, and immunohistochemistry indicated that the tumors were all GISTs.

At the same time, gene sequencing (according to the Sanger sequencing method) was performed on two large tumors in the abdominal wall and pelvis. The pelvic tumors had KIT exon 11: W557_K558del and KIT exon 13: V654A mutations. The abdominal wall nodule had a KIT exon 11: W557_K558del mutation. Postoperatively, the

patient stopped taking the drug due to the clinical trial and their wishes.

In March 2021, the patient's abdominal CT scan revealed multiple nodules in the liver S2 segment, the upper edge of the spleen, and both lungs, suggesting a high possibility of metastasis. The patient started treatment with imatinib mesylate (600 mg QD). The CT scan on September 9, 2021, showed that the largest nodule in both lungs was 35 mm × 19 mm. The intrahepatic multiple hypodense nodular foci mostly located in the S2 segment were smaller than before, with a maximum diameter of approximately 2.0×1.3 cm. Soft tissue masses were seen in the pelvic and abdominal cavities, with an unclear boundary with the adjacent intestines and a maximum diameter of approximately 6.4×4.6 cm, showing uneven enhancement. On October 11, 2021, an abdominal CT re-examination revealed a soft tissue mass below the stoma of the right lower abdomen, with a maximum cross-section of 5.6 cm × 5.2 cm. The maximum interface of the mass in the liver S3 segment was 2.1 cm × 2.6 cm, which was larger than before, and the maximum diameter of the soft tissue mass in the pelvic and abdominal cavities was 9.0×5.8 cm, which was markedly larger than before.

Considering the marked disease progression, the patient was again treated with ripretinib (150 mg QD) on October 14, 2021. The CT re-examination on December 12, 2021, showed that the maximum interface of the mass under the right lower abdominal stoma was 5.4 cm × 5.5 cm, which was slightly larger than the previous interface. The diameter of the nodules in the S2 segment was approximately 1.2 cm, and the pelvic-abdominal mass was 6.3 cm × 4.7 cm, which was slightly smaller than before. The soft tissue masses in the pelvis, multiple hypodense foci in the liver, and extremely hypodense shadows in the upper pole of the spleen were significantly smaller than before, and the multiple peritoneal nodules were smaller than before and had partially disappeared. Chest CT revealed that the soft tissue masses at the anterior basal segment of the right lower lobe and the posterior basal segment of the left lower lobe were smaller than before and had partially disappeared. There were no significant changes in the remaining bilateral lung nodules.

On March 4, 2022, a CT re-examination of the abdominal pelvic cavity indicated that the maximum cross-section of the soft tissue mass below the right lower abdominal ostomy was 7.3 cm × 7.1 cm, which was slightly larger than before. The largest intra-abdominal mass was 6.3 cm × 4.5 cm, which was smaller than before, and the mass in the S2 segment of the liver was larger than before, with a diameter of approximately 1.7 cm. Imaging diagnosis showed that the pelvic-abdominal soft tissue mass was smaller than before, the soft tissue mass under the right lower abdominal fistula was larger than before, a portion of the multiple hypodense foci in the liver were larger than before, and the extremely hypodense shadows in the upper pole of the spleen were smaller than before. The hypodense shadow in the posterior left lobe of the liver was not observed. The remaining features were approximately the same as before.

The patient's disease treatment process was reviewed. After two surgical treatments, the first-line tyrosine kinase inhibitor (TKI) imatinib (survival benefit of 8 years and 5 months), and the second-line drug sunitinib (survival benefit of 3 years and 2 months) were used successively, and the patient could not tolerate treatment with the third-line drug (regorafenib). After the patient entered fourth-line clinical treatment with ripretinib, the overall tumor evaluation was SD at 4 months, and the overall tumor did not progress. Due to the heterogeneity of recurrent metastatic tumors, the tumor with the largest volume in the abdominal wall was liquefied and necrotic, manifested as tissue edema, and exhibited an increased diameter. The tumors in the pelvic and abdominal cavities displayed significant regression and remission, and the tumor that originally had no anatomical gap with the intestinal tube showed an anatomical boundary, which provided a therapeutic opportunity for surgical resection. After surgery, case studies and genetic testing confirmed the heterogeneity of the abdominal wall and pelvic tumors. The abdominal wall tumors had C-KIT exon 11 deletion mutations, which tended to be primary mutations, while the pelvic tumors had C-KIT exon 11 deletion mutations and missense mutations in exon 13, which tended to be secondary mutations.

Approximately 3 months after surgery, the patient had pelvic and abdominal tumor recurrence and liver and lung metastases, and treatment with imatinib was ineffective. Ten months after surgery, ripretinib was administered again, and multiple target lesions in the whole body again showed heterogeneity. The pelvic and abdominal tumors under the stoma grew slowly while the remaining lesions in the abdomen, abdominal wall, liver, and lungs became stable or entered remission, and the overall systemic condition was effectively controlled. The whole course of treatment lasted for 23 years. The advanced stromal tumors remain under control without significant tumor progression after 2–3 years of postline therapy, ensuring the survival quality of the patient. This is a rare case of multiline treatment for

advanced GIST.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

GISTs are the most common mesenchymal tumors of the digestive system and occur most frequently in the stomach (50–60%), followed by the small intestine (30–35%) (1-2). It is generally believed that the prognosis of GISTs is poor, and there are currently few reports on GISTs (3-6). In 2006, Miettinen *et al.* (5) reported on the clinical, pathological, and molecular biological characteristics of 906 GIST cases, which represents a relatively large and comprehensive cohort of GIST studies.

For tumors driven by gene mutations, such as GISTs, molecular testing plays an important role in predicting the efficacy of targeted drugs (7). According to the *Diagnosis and Treatment Guidelines of Gastrointestinal Stromal Tumors of the Chinese Society of Clinical Oncology (CSCO) 2021*, GIST patients should undergo genetic testing before receiving targeted therapy. However, the application rate of molecular testing in China is still low. In the case described in this study, the patient's initial disease onset was in 1999, when medical knowledge regarding GISTs and genetic testing was insufficient. However, the patient only underwent CT-guided tumor tissue biopsy and genetic testing after the failure of imatinib treatment in 2017 and genetic testing of the two largest tumors in the specimens after surgical treatment in December 2020. The temporal and spatial heterogeneity of secondary mutations in tumors cannot be fully evaluated, and there are many limitations for the precise and timely treatment of targeted drugs (8,9). Especially for postline therapy with a high tumor burden, accurate and comprehensive pathological examination and genetic testing are usually prognostic factors for GIST patients (10-12).

The primary mutation site in this case was a mutation in exon 11 of the KIT gene, which is the most common primary mutation site in GISTs (10,12). As gene sequencing was not performed in the early stage, according to the standard treatment with the first-line and second-line drugs, following the detection of a clear secondary mutation in the postline gene, the precise diagnosis and treatment model based on the driver gene was performed for the mutation at multiple sites. For targeted GIST therapy, it is necessary to combine line therapy and precise therapy (13), which requires medical care for the entire course of patient management with regular follow-up and tumor evaluation. The effective control of adverse drug reactions and dose management of TKIs can help extend the duration of drug treatment, maximize the benefits of drug treatment, select the appropriate timing of surgical treatment, combine and transform adjuvant therapy with conversion therapy, and prolong the survival of patients (14-21).

Conclusions

Type II TKI drugs, such as ripretinib and avapritinib, have produced greater than traditionally expected therapeutic effects for the treatment of many advanced GISTs. Ripretinib has the unique characteristics of a dual inhibition mechanism consisting of a switch pocket and switch key in the GIST molecular conformation and good drug tolerance, which provides hope and options for surgical opportunities in postline targeted therapy and conversion therapy. At the same time, the combined application of types I and II TKIs has also been explored in numerous clinical treatments. It is expected that an increase in new drugs and programs will benefit GIST treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1361/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1361/coif). The authors have no conflicts of interest 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. All procedures performed in this study were in accordance with the ethical

standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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