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Case Report

CASE REPORT

Apatinib treatment for unresectable gastrointestinal stromal tumor with synchronous gastric cancer

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Abstract

Nearly one-fifth of patients diagnosed with gastrointestinal stromal tumors (GISTs) simultaneously experience a second primary tumor. In particular, coexistence of gastric GISTs and gastric cancer is relatively more common. However, the optimal treatment for advanced GIST with gastric cancer is largely unknown. We report a case of simultaneous occurrence of gastric GIST and gastric cancer that benefited from apatinib. After first-line imatinib and S-1 treatment for 6 months, the GIST and the gastric cancer both progressed. The patient was then treated with apatinib, exhibiting a partial response (PR) both in the GIST and the gastric cancer at 7 months, and continuous PR so far with well-controlled toxic effects of hypertension. Progression-free survival reached 10 months. In view of the relatively high incidence of advanced GIST with synchronous gastric cancer, therapy to simultaneously treat the two kinds of tumors is urgently needed. Apatinib provides promising and well-tolerated therapy for GISTs with synchronous gastric cancer refractory to chemotherapy combined with imatinib.

Key words: GIST; gastric cancer; apatinib; stromal tumor

Introduction

The most common mesenchymal tumors in the gastrointestinal tract are gastrointestinal stromal tumors (GISTs), primarily located in the stomach.[1] With extensive development of gastrointestinal endoscope and computerized tomography (CT), GISTs with other primary tumors have been diagnosed more commonly, either metachronously or synchronously. Recently, a systematic review of 32 candidate articles including 19 627 patients with GIST identified that ~14% of GISTs coexisted with second primary tumors, primarily located in the gastrointestinal tract.[2] In particular, several studies have reported that about 10%–25% of gastric GISTs present with gastric cancers synchronously, far more frequently than other cancers, probably because of the same carcinogenic environment.[3,4]

For metastatic or unresectable GISTs, imatinib is the first-line choice, the second-line treatment is sunitinib, which is then followed by regorafenib treatment. As for unresectable GISTs with synchronous gastric cancer, a

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combination of imatinib and chemotherapy is usually recommended. However, after any failure of imatinib and chemotherapy treatment in those patients, there is no standard therapy and few clinical experience reports of medical treatment. Most patients, especially elderly people, may be unable to tolerate chemotherapy in combination with sunitinib or regorafenib. Thus, an effective and well-tolerated second-line therapy that could simultaneously treat GIST and gastric cancer is urgently needed.

The small molecule tyrosine kinase inhibitor apatinib can repress the kinase activities of VEGFR2, PDGFR-β, c-KIT, and c-Src, with encouraging therapeutic effects across many tumors. It was approved as a subsequent-line therapy for advanced gastric cancer by the China Food and Drug Administration (CFDA) in 2014.[5] Recently, we first reported a unique case with metastatic GISTs that responded to apatinib strongly.[6] Here, we present a case with unresectable gastric GIST with synchronous gastric cancer that derives particular benefit from apatinib in second-line therapy, demonstrating the potential efficacy of apatinib in the treatment of specific types of GISTs with synchronous gastric cancer.

Case presentation

A 75-year-old man was found to have a large mixed echogenic mass with no symptoms in the left upper abdomen by ultrasound during a routine examination in November 2017. Abdominal CT with intravenous contrast demonstrated a huge mixed echogenic mass about 12.0 cm×9.6 cm×9.4 cm in size on the lateral side of the gastric fundus, and wall thickening about 1.0 cm on the posterior wall of the gastric antrum. The mass projected into the stomach cavity with serosal invasion, and oppressed the pancreas, spleen, and splenic artery-vein. Nodular lesions were also seen over the omentum and hepatogastric ligament.

Upper gastrointestinal endoscopy was then performed, which showed an underlying huge protruding mass over the gastric fundus and a tumor arising from the gastric antrum. The histopathological diagnosis for the submucosal mass was fusiform GIST. Immunohistochemistry indicated high expression of CD34, DOG-1, and CD117, while staining of S-100 was negative. The tumor in the gastric antrum was a low differentiated adenocarcinoma mixed with signet ring cancer.

The patient was diagnosed with unresectable gastric GIST with synchronous gastric cancer of large tumor size (>10 cm) and closely adhering to surrounding tissues. The multidisciplinary team recommended medical treatment first for the patient and then investigation of the surgical strategy after any tumor regression. Mutation detection indicated c-KIT exons (9, 11, 13, and 17) and PDGFR-α exons (12, 14, and 18) without mutations, and immunohistochemistry indicated positive expression of succinate dehydrogenase B (SDHB).

Beginning in January 2018, the patient was treated with imatinib (400 mg/day) and S-1, an oral fluoropyrimidine (25 mg twice a day). The major side effects were dental ulcer and peeling, which limited the increase of the dose. Disease progression of the GIST (about 15.6 cm×12.4 cm×10.6 cm in size) and the gastric cancer (about 2.2 cm in thickness) both occurred with abdominal dull pain and loss of weight after 6 months of treatment (Fig. 1A). Sunitinib and regorafenib have been used as second- and third-line therapy for advanced GISTs. However, although a combination of sunitinib/regorafenib and chemotherapy such as paclitaxel might restrict progression of the two tumors, the patient refused this combination because of the high price of sunitinib and regorafenib, and also fear of the side effects of this combined therapy.

In the meantime, a new clinical trial (ChiCTR1800020407) had begun in which apatinib was given to patients with advanced GIST in subsequent-line treatment. A patient with metastatic GIST already enrolled in that trial was observed to benefit from apatinib treatment for at least 4 months after failure of imatinib and sunitinib.[6] As apatinib has been approved as a subsequent-line therapy for patients with advanced gastric cancer, it seemed to be a suitable drug for the patient in our present study. Thus, beginning in August 2018, the present patient started oral apatinib with a reduced dose of 250 mg daily. CT reexamination in March 2019 showed the partial response (PR) produced by apatinib, decreasing the tumor size to 10.8 cm×9.6 cm×9.4 cm besides the GIST density (Fig. 1B). Continuous PR was also confirmed by CT reexamination in June 2019 (Fig. 1C). The gastric cancer also exhibited a PR (about 1.3 cm in thickness) and continuous PR in the last two follow-up visits (Fig. 1B and 1C). Progression-free survival for the two tumors reached 10 months. The dull pain in the patient's abdomen went away, and the weight loss did not continue.

During apatinib treatment, the primary side effect was hypertension of Grade I-II, according to the Common Terminology Criteria for Adverse Events (version 4.03), which was well controlled after drug treatment. No bleeding was observed. Despite the drug being well tolerated with no severe side effects, the patient refused to increase the dose of apatinib due to budget constraints.

Discussion

GIST is a common mesenchymal tumor of the digestive tract. Adults with median ages around 60 years are more likely to develop GISTs.[7] About 75%–80% of GISTs have c-KIT mutations, and PDGFR-α mutations occur in ~10% of GISTs, while mutations in the two genes are mutually exclusive. Only 10%–15% of GISTs are referred to as wild-type GISTs without c-KIT and PDGFR-α mutations.[8] Among these wild-type GISTs, a small subset with SDH deficiency exhibit primary resistance to imatinib therapy.[9] Patients with recurrence, metastatic or

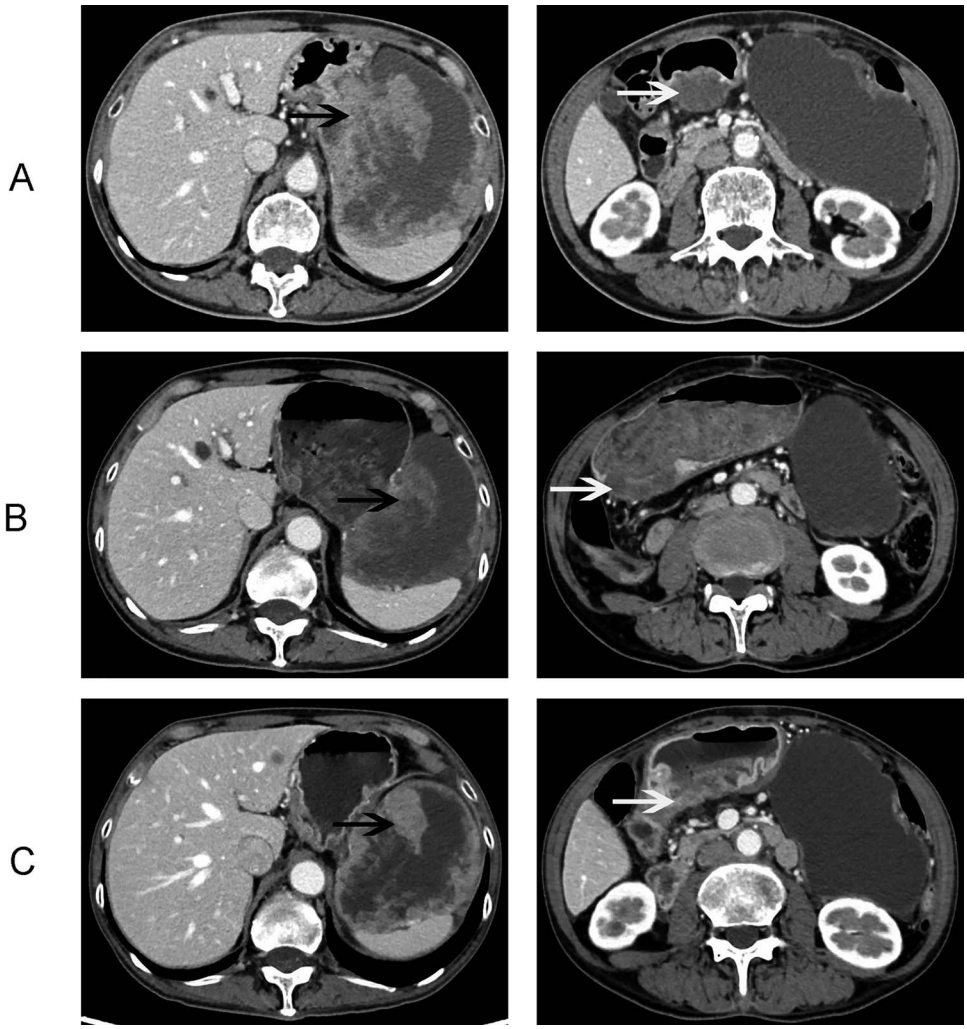

Figure 1. Apatinib treatment reduced the tumor volume of gastrointestinal stromal tumor and synchronous gastric cancer. Abdominal computed tomography scans showing a huge mixed echogenic GIST (black arrow) and the gastric cancer (white arrow) before apatinib treatment (A) to a partial response (B), and continuous PR (C) in the last two routine follow-up visits. The tumor density of the GIST was also dramatically reduced after apatinib treatment.

unresectable GISTs are often treated with KIT/PDGFR-α tyrosine kinase inhibitors, mainly the first-line imatinib and the subsequent-line sunitinib and regorafenib.

Apatinib is a potent VEGFR2 inhibitor, and can also inhibit the kinase activities of c-KIT, c-Src, and PDGFR-β,[5] demonstrating a potential therapeutic effect in a broad range of tumors from gastric cancer, lung cancer, and colorectal cancer.[10] Recently, we first reported a case of metastatic GIST in which stable disease was maintained for at least 8 months during apatinib treatment.[6] Now, we present a second case of GIST that responded to apatinib treatment for more than 10 months after failure of imatinib treatment. No mutations in c-KIT or PDGFR-α have been found in the present GIST case, indicating that apatinib might inhibit the progression of GISTs independent of c-KIT and PDGFR-α mutation status.

Several studies have shown that almost one-fifth of patients with GISTs experience synchronous cancers, mainly originating from the stomach and colorectum.[2–4] Whether the synchronicity of gastrointestinal epithelial and stromal tumors is connected by a causal relationship or just an incidental association remains unclear. So far, researchers have not found a common genetic mutation underlying gastrointestinal cancers and GISTs. The reason might be that stroma and epithelium are in the same carcinogenic environment.[11]

GIST patients with synchronous gastrointestinal cancers have much worse prognoses than those without.[4,11] Thus, an effective and well-tolerated therapy to treat this subset of GISTs would be of important clinical value. For the patient in this case report, imatinib was recommended as first-line therapy after diagnosis with wild-type GIST without SDH deficiency, and S-1 was added to treat gastric cancer. After failure of the first-line treatment, we were excited to observe that apatinib could simultaneously inhibit progression of both GIST and gastric cancer. Apatinib was also reported to be active

as a third-line treatment for colorectal cancer.[12] Thus, for the particular subset of GISTs with synchronous gastrointestinal cancers, apatinib treatment might be a good choice.

Conclusions

For patients with GISTs refractory to imatinib, particularly in the subset with synchronous gastric adenocarcinoma, apatinib shows a unique advantage of activity in both histologies. In consideration of the significant proportion of GISTs with synchronous gastrointestinal cancers, our approach with apatinib gives a future direction for clinical treatment.

Ethics statement

This study was approved by the Institutional Review Board of West China Hospital (ChiECRCT-20170095). Trial registration: ChiCTR, ChiCTR1800020407. Registered 28 December 2018 -Retrospectively registered, http://www.chictr.org.cn. Written informed consent was obtained from the patient for publication of the findings of this case report.

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Conflict of interest

None declared.

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