

OPEN

# A Case Report of Gastrointestinal Hemorrhage and Perforation During Apatinib Treatment of Gastric Cancer

Xiao-Fen Li, MD, Yi-Nuo Tan, MD, Ying Cao, MD, Jing-Hong Xu, MD, Shu Zheng, MD, and Ying Yuan, MD, PhD

**Abstract:** Apatinib is a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor-2, which shows good efficacy and safety in clinical trials for chemotherapy-refractory gastric cancer patients. Till now, there is no case report after apatinib came in the market.

We presented a 55-year-old Chinese woman with advanced gastric cancer, who received apatinib after failure of second-line chemotherapy. On the 19th day of apatinib administration, she suffered from gastrointestinal hemorrhage. Then, her condition rapidly deteriorated to gastrointestinal perforation. Although the patient received timely medical and surgical treatment, she finally died of septic shock.

Although apatinib shows exciting efficacy and good tolerance in phase II and III clinical trials, this novel targeted drug should be prescribed carefully and close clinical monitoring is needed when using it.

(*Medicine* 94(39):e1661)

**Abbreviations:** AEs = adverse events, CT = computed tomography, ENFTP = endoscopically nasojunal feeding tube placement, FISH = fluorescence in situ hybridization, ICU = intensive care unit, IHC = immunohistochemistry, MODS = multiple organ dysfunction syndrome, OR = odds ratio, PFS = progression-free survival, PPI = proton pump inhibitor, RECIST = Response Evaluation Criteria in Solid Tumors, rh-GCSF = recombinant human granulocyte-colony stimulating factor, RR = relative risk, SD = stable disease, SFDA = State Food and Drug Administration, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor, VEGFR-2 = vascular endothelial growth factor receptor-2, WHO = World Health Organization.

Editor: Raj Kumar.

Received: June 17, 2015; revised: August 24, 2015; accepted: August 30, 2015.

From the Department of Medical Oncology (X-FL, Y-NT, YC, YY); Department of Pathology (J-HX); and Key Laboratory of Cancer Prevention and Intervention of Ministry of Education, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China (SZ, YY).

Correspondence: Dr Ying Yuan, Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jie-Fang Road, Hangzhou, Zhejiang 310009, China (e-mail: yuanying1999@zju.edu.cn).

Dr Shu Zheng, Key Laboratory of Cancer Prevention and Intervention of Ministry of Education, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China (e-mail: zhengshu@zju.edu.cn).

The authors declare no competing interests.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial License, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be used commercially.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001661

## INTRODUCTION

Gastric cancer is the fifth most common malignancy in the world and ranks as the third leading cause of cancer-related death.<sup>1</sup> According to the statistics of World Health Organization (WHO), more than 40% of cases occur in China.<sup>1</sup> Despite rapid progress in cancer diagnostic and therapeutic techniques, there is no standard third-line treatment for advanced gastric cancer so far. Apatinib is an oral tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor-2 (VEGFR-2), which shows efficacy as third-line treatment in gastric cancer patients.<sup>2</sup> In December 2014, China State Food and Drug Administration (SFDA) approved apatinib for the treatment of chemotherapy-refractory gastric cancer patients.

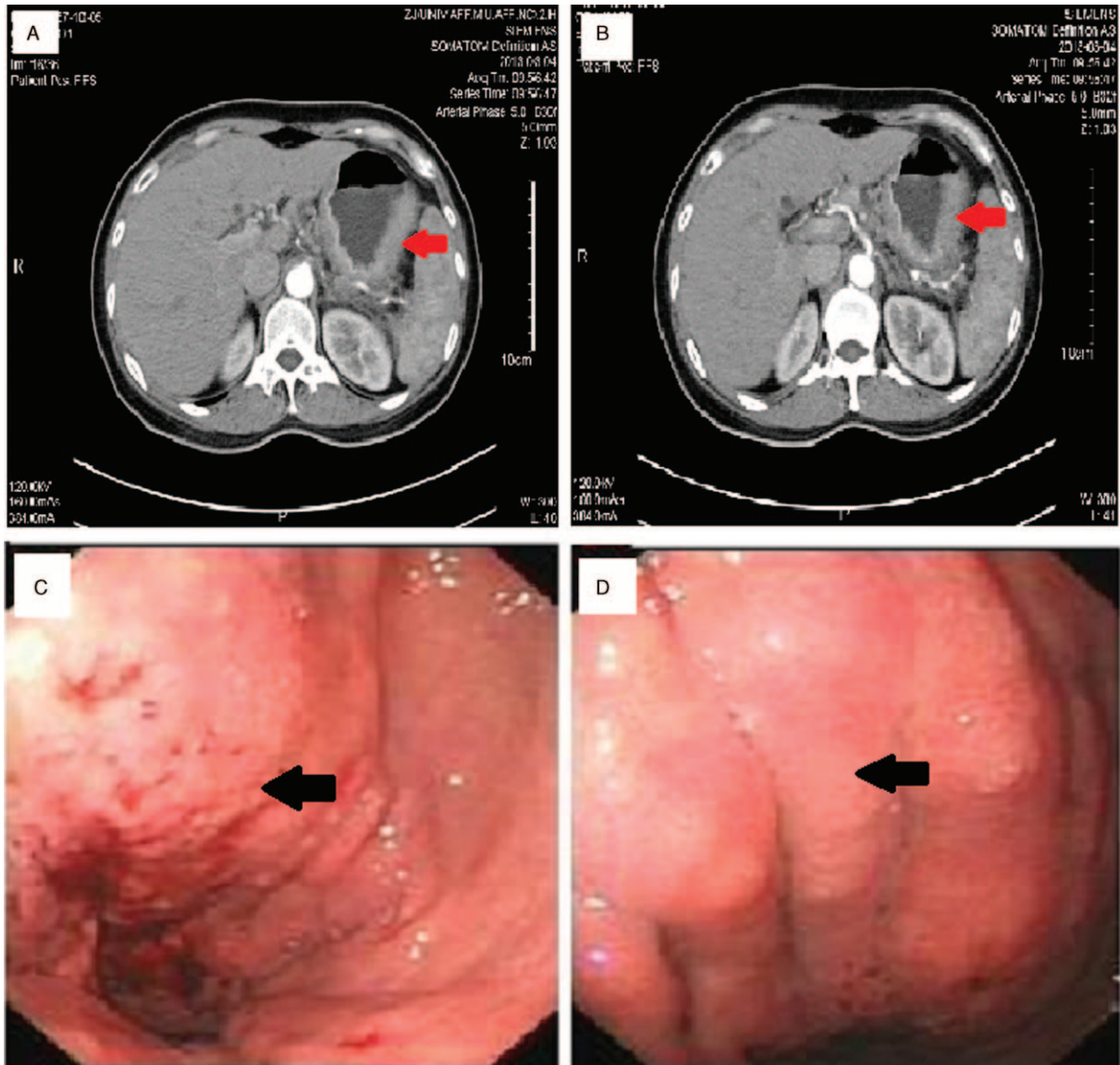
Herein we reported a case of a 55-year-old Chinese woman with advanced gastric cancer, who received apatinib after failure of second-line chemotherapy. During apatinib administration, the patient suffered from gastrointestinal hemorrhage and perforation that led to septic shock.

## CASE PRESENTATION

A 55-year-old Chinese woman, diagnosed with gastric adenocarcinoma, was referred to the Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) in March 2013 (Figures 1 and 2). Neither abdominal mass nor superficial lymph node was palpable. Moreover, the rest of the physical examination was unremarkable. Chest and abdominal computed tomography (CT) scans did not reveal any obvious distant metastasis. Surgery was performed on March 12, 2013, after preoperative evaluation. Many white nodules were distributed in the abdominal cavity, which were confirmed to be poorly differentiated adenocarcinoma by intraoperative frozen-section examination. Since there were extensive abdominal metastases, the surgery was stopped without gastrectomy. Postoperative pathology showed signet-ring cell carcinoma of peritoneal nodule (Figure 3). The result of immunohistochemistry (IHC) was *CerbB-2* 2+, *Ki67*+, *Syn*−, *CgA*−. Moreover, fluorescence in situ hybridization (FISH) examination indicated negative of *CerbB-2* gene amplification.

Diagnosed with gastric cancer with extensive abdominal metastases, the patient received 6 cycles of first-line palliative chemotherapy (oxaliplatin 100 mg/m<sup>2</sup> on day 1 and S-1 60 mg bid on day 1 to day 14), repeated every 3 weeks. Imaging examination after the second, fourth, and sixth cycle showed slight shrink of gastric tumor, which indicated stable disease (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST). The patient tolerated chemotherapy very well. After first-line chemotherapy, the patient was administered oral S-1 as a maintenance treatment.

In June 2014, 10 months after the end of first-line chemotherapy, the patient suffered from cardiac obstruction. Endoscopically nasojunal feeding tube placement (ENFTP)

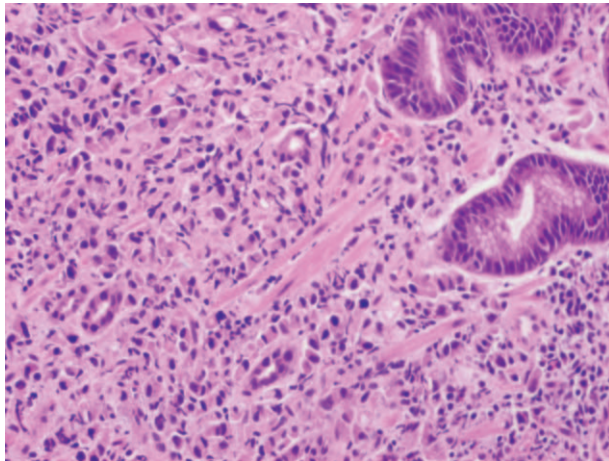


**FIGURE 1.** Enhanced abdominal CT scan, gastric endoscopy. (A, B) On March 4, 2013, enhanced abdominal CT scan revealed extensive thickening of gastric body and antrum wall (arrows). (C, D) Gastric endoscopy showed mural thickening and stiffness with multiple erosions in the gastric body (arrows), indicating linitis plastica. CT, computed tomography.

was performed by the gastroenterologist. Moreover, the patient received 5 cycles of second-line chemotherapy consisting of albumin-bound paclitaxel  $130\text{ mg/m}^2$  on day 1 and 8, and oxaliplatin  $100\text{ mg/m}^2$  on day 2, repeated every 3 weeks. Obstructive symptoms were significantly relieved after 2 cycles of chemotherapy, and the feeding tube was removed. The patient obtained SD on CT scans after 6 cycles of chemotherapy. Grade 4 neutropenia occurred and treated with recombinant human granulocyte-colony stimulating factor (rh-G-CSF) (Table 1).

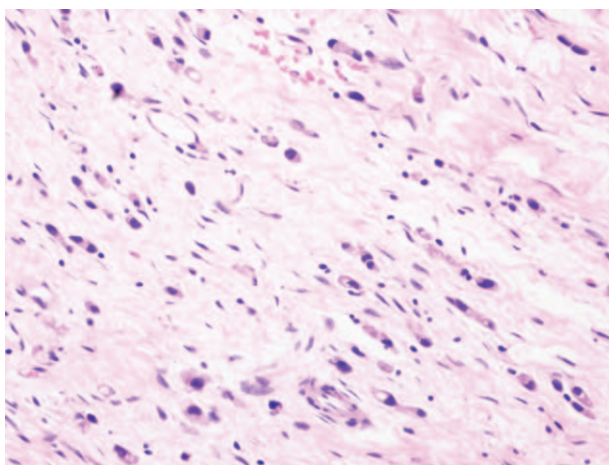
In November 2014, 2 months after termination of second-line chemotherapy, the disease progressed again. Best supportive care was given. But incomplete gastrointestinal obstruction occurred repeatedly. On December 13, 2014, a new oral-targeted drug for gastric cancer, apatinib, was approved by China

SFDA. On December 20, 2014, we prescribed apatinib  $850\text{ mg}$  once a day for the patient. However, the drug could not relieve the obstruction symptoms including nausea, vomiting, and abdominal pain. The patient's blood pressure rose mildly after taking apatinib. On the 19th day of apatinib administration, the patient started to spit blood streak and clot, and fecal occult blood test was positive, whereas blood coagulation spectrum was normal. Hematemesis was not relieved after 4 days of standard medical treatment, including fasting, parenteral nutrition, and proton pump inhibitor (PPI) prescription. On January 13, 2015, we had to stop apatinib administration. In the night of January 13, 2015, the patient complained of sudden severe abdominal pain with nausea and vomiting, and emergency erect abdominal plain radiograph indicated gastrointestinal obstruction without subphrenic free air. Regular analgesic and



**FIGURE 2.** Pathology of gastric biopsy. In March 2013, gastric biopsy pathology indicated gastric signet-ring cell carcinoma (hematoxylin and eosin, magnification 100×).

spasmolytic therapy was administrated, which unfortunately showed little effect. And 47 minutes later, the patient presented with unstable hemodynamics. Antishock treatment was given immediately. Meanwhile, enhanced abdominal CT scan showed a large amount of ascites and gastric mass with peritoneal metastatic lesions (Figure 4A). Acute surgical consultation was held, and the patient was diagnosed with gastrointestinal perforation, acute diffuse peritonitis, and septic shock. Then, she was transferred to the Department of General Surgery promptly. Emergency operation was carried out. There was approximately 3000 mL of purulent ascites with excrement stink in the abdomen. A perforated ulcer about 1 cm in diameter existed on the anterior gastric wall. Apart from this, there were many miliary nodules distributing in the abdominal cavity and a large tumor in the ileal lumen, the pathological diagnosis of which was metastatic signet-ring cell carcinoma (Figure 4B). Surgeons irrigated her abdomen with normal saline, performed



**FIGURE 3.** Postoperative pathology of peritoneal nodule. In March 2013, postoperative pathology revealed signet-ring cell carcinoma of peritoneal nodule (hematoxylin and eosin, magnification 100×). Immunohistochemistry result was *CerbB-2* 2+, *Ki67*+, *Syn*−, *CgA*−. Fluorescence in situ hybridization analysis indicated negative of *CerbB-2* gene mutation.

**TABLE 1.** Medical Information About the Patient

Item	Description
Age	55 years old
Sex	Female
Ethnicity	Chinese
History	Being healthy before
Family history	No cancer or other hereditary diseases in family members
Physical examination	Unremarkable
Pathological examination	Gastric signet-ring cell carcinoma

enterolysis, repaired perforated gastric wall, and resected the ileal tumor. The patient was transferred to the surgical intensive care unit (ICU) after operation. But shock symptoms continued and developed to multiple organ dysfunction syndrome (MODS). The patient finally died on February 23, 2015.

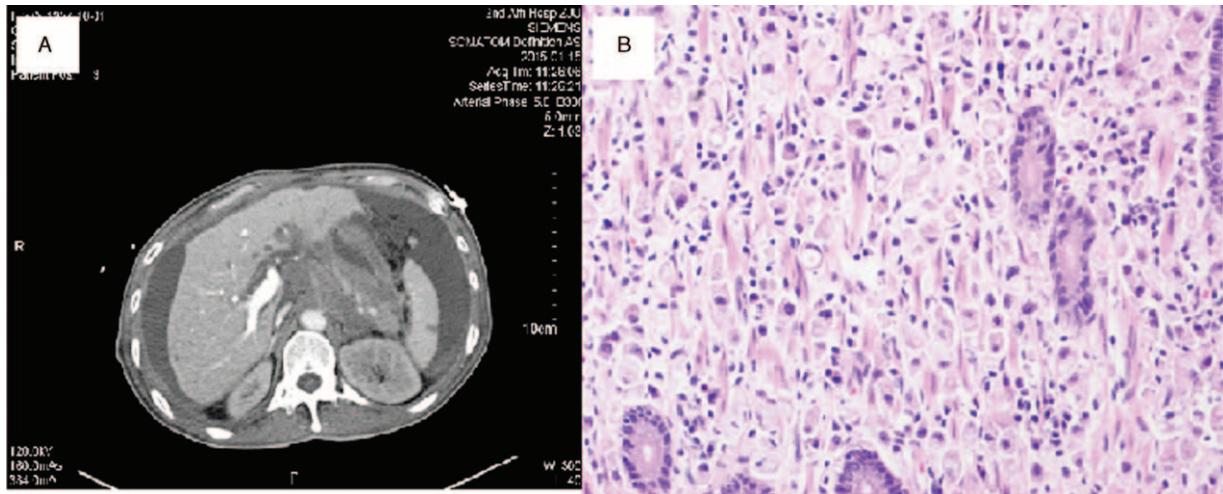
### DISCUSSION

Apatinib is a novel, oral small-molecule VEGFR-2 inhibitor, which can suppress tumor angiogenesis.<sup>2,3</sup> Phase II and III studies of apatinib have shown exciting efficacy and good safety in Chinese gastric patients who have failed at least 2 chemotherapeutic regimens.<sup>4,5</sup> In the phase III study of apatinib,<sup>5</sup> 273 patients were randomly assigned to oral apatinib group or placebo group at a ratio of 2 : 1. Patients with bleeding tendency were excluded. The results showed that patients receiving apatinib had significantly longer median overall survival (195 vs 140 days;  $P < 0.016$ ) and longer median progression-free survival (PFS) (78, vs 53 days;  $P < 0.0001$ ) compared with those receiving placebo. Both in the phase II and III studies of apatinib,<sup>4,5</sup> the 3 most common adverse events (AEs) were hypertension, hand-foot syndrome, and proteinuria. But there was no significant difference in severe AEs (such as gastrointestinal massive hemorrhage and perforation) between the 2 groups. According to current studies of apatinib in gastric cancer patients, AEs were manageable and reversible.<sup>2,4,5</sup> Patients with bleeding tendency were excluded in the 2 clinical trials.

The patient in our study had mildly raised blood pressure after taking apatinib. Moreover, she did not experience other common AEs such as hand-foot syndrome, proteinuria, and coagulation disorder. However, upper gastrointestinal bleeding occurred on the 19th day of apatinib administration. Also, the patient's condition rapidly deteriorated to gastrointestinal perforation. Despite timely medical and surgical treatment, she finally died of septic shock.

The common causes of upper gastrointestinal bleeding are peptic ulcer, acute gastritis, esophageal varices, gastrointestinal malignancy, etc.<sup>6</sup> Additionally, the main causes of upper gastrointestinal perforation are peptic ulcer, necrotic or ulcerated malignancy, iatrogenic, and traumatic injuries.<sup>7</sup> Considering our patient's disease and history of drug use, we thought that the most possible causes of her upper gastrointestinal bleeding and perforation included drug resistance and cancer progression, adverse effect of apatinib, and combined results of the former 2 reasons.

First of all, the patient's clinical symptoms were not relieved after 19 days of apatinib use. Later, abdominal CT scan and emergency surgery proved apatinib resistance and



**FIGURE 4.** Enhanced abdominal CT scan and postoperative pathology of intestinal mass. (A) On January 13, 2015, enhanced abdominal CT scan showed a large amount of ascites and gastric mass with peritoneal metastatic lesions. (B) Postoperative pathology of ileal mass revealed metastatic signet-ring cell carcinoma, without any area of necrosis (hematoxylin and eosin, magnification 100 $\times$ ). CT, computed tomography.

cancer progression, which could lead to tumor bleeding. A retrospective study conducted by Maluf-Filho et al<sup>8</sup> showed that cancer was the main cause of gastrointestinal bleeding in patients with upper gastrointestinal tract cancer, accounting for 84.4% of all causes. In our case, cancer-related bleeding could probably be part of the reason for gastrointestinal bleeding. But, considering the sudden occurrence and rapid deterioration of hemorrhage, cancer progression would be unlikely the only cause.

Furthermore, as a VEGFR-2 inhibitor, the adverse effects of apatinib possibly include gastrointestinal hemorrhage and perforation. Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) are critical factors of VEGF pathway, which plays a vital role in tumor angiogenesis. Both VEGF antibodies and VEGFR inhibitors can suppress the VEGF pathway and show clinical efficacy in cancer treatment.<sup>9</sup> Studies have indicated that VEGF antibodies such as bevacizumab and aflibercept had a higher risk of hemorrhage and perforation events than control drugs.<sup>10–12</sup> A meta-analysis including 17 clinical trials observed a significantly increased risk of gastrointestinal perforation in patients treated with bevacizumab compared with control medications (relative risk [RR] 2.14, 95% confidence interval [CI] 1.19–3.85,  $P=0.011$ ).<sup>11</sup> Similarly, another meta-analysis including 8 clinical trials demonstrated that patients treated with aflibercept had a significantly higher risk of gastrointestinal perforation than controls (odds ratio [OR] 3.76, 95% CI 1.94–7.25,  $P<0.001$ ).<sup>12</sup> Taking VEGFR inhibitors into consideration, a meta-analysis conducted by Qi et al, including 27 clinical trials, did observe that VEGFR-TKIs (not including apatinib) were associated with a significantly increased risk of all-grade hemorrhagic events (RR 1.67, 95% CI 1.19–2.33,  $P=0.003$ ), but not related with gastrointestinal hemorrhage (RR 0.54, 95% CI 0.12–2.42,  $P=0.42$ ).<sup>13</sup> Moreover, another recent meta-analysis including 20 clinical trials did not observe increased risk of gastrointestinal perforation in patients using VEGFR-TKIs (OR 2.99, 95% CI 0.85–10.53,  $P=0.089$ ).<sup>14</sup> But these analyses did not investigate apatinib, which is a novel VEGFR-TKI. Phase II and III clinical trials of apatinib in gastric cancer excluded patients with bleeding tendency, and neither of them reported gastrointestinal

bleeding or perforation events associated with apatinib.<sup>4,5</sup> Apart from this, there has been no report on severe AEs of apatinib since it came into the market. Therefore, we can see that there is some evidence proving the association between VEGF pathway inhibitors and severe gastrointestinal AEs (hemorrhage and perforation), but the risk of VEGFR-TKI including apatinib is not clear. In another word, apatinib might be the cause of our patient's gastrointestinal hemorrhage and perforation, but this opinion lacks adequate evidence. Further studies and reports of apatinib are warranted.

In summary, drug resistance and cancer progression, as well as adverse effect of apatinib, could probably be the reasons for our patient's bleeding and perforation, but we cannot determine the direct and real reason according to existing studies and experience. But at least, we have learned that apatinib should be administered with caution, whose risk of gastrointestinal hemorrhage and perforation needs further investigation. We wrote this report to share experience with oncologists, since apatinib has been seldom used in clinical practice so far.

It is worth mentioning that this patient obtained a relatively long PFS time of first-line chemotherapy (141/2 months), which may in part attribute to S-1 maintenance therapy. S-1, which is available for advanced gastric cancer in European and Asian countries, is an oral anticancer drug that combines tegafur with gimeracil and oteracil.<sup>15</sup> A randomized phase III clinical trial conducted by Boku et al<sup>16</sup> indicated that S-1 was noninferior to 5-fluorouracil as first-line treatment in metastatic gastric cancer. Chen et al<sup>17</sup> performed a case-control study to investigate the efficacy of S-1 maintenance chemotherapy in advanced gastric cancer. The results showed that S-1 group had significantly higher disease control rate than optimal supportive care group (73.3% vs 46.7%;  $P<0.05$ ,  $n=60$ ), but the 2 groups' PFS and overall survival were not significantly different. To date, there have not been large-scale clinical trials evaluating efficacy of S-1 as maintenance treatment in advanced gastric cancer. In addition, there is no standard maintenance strategy worldwide for metastatic gastric cancer. Thus, we present this case to share clinical experience in maintenance treatment of gastric cancer.

There are some limitations of this case report. First of all, the intrinsic methodological limitations of case reports exist in our study as well, including lack of sampling, low level of clinical evidence, etc. Second, as discussed above, we cannot determine the real reason for the patient's gastrointestinal bleeding and perforation. Moreover, this case lacks a literature review, because there is no similar study so far.

### CONCLUSIONS

Apatinib is a novel TKI targeting VEGFR-2, which shows good efficacy and tolerance in clinical trails as third-line treatment for metastatic gastric cancer. But oncologists should administer this drug carefully, and strengthen the clinical monitoring when using it. Moreover, S-1 may be a good choice for maintenance treatment of advanced gastric cancer, which needs further randomized case-control studies.

### ACKNOWLEDGMENTS

*Consent: Written informed consent was obtained from the patient's family for publication of this case report and accompanying images.*

### REFERENCES

- World Health Organization [homepage on the internet]. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available at: <http://globocan.iarc.fr/old/Fact-Sheets/cancers/stomach-new.asp>. Accessed May 18, 2015.
- Geng R, Li J. Apatinib for the treatment of gastric cancer. *Expert Opin Pharmacother*. 2015;16:117–122.
- Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. *Cancer Sci*. 2011;102:1374–1380.
- Li J, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol*. 2013;31:3219–3225.
- Qin S. Phase III study of apatinib in advanced gastric cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2014;32:5s(Suppl; abstr 4003).
- Wilkins T, Khan N, Nabh A, et al. Diagnosis and management of upper gastrointestinal bleeding. *Am Fam Physician*. 2012;85:469–476.
- Furukawa A, Sakoda M, Yamasaki M, et al. Gastrointestinal tract perforation: CT diagnosis of presence, site, and cause. *Abdom Imaging*. 2005;30:524–534.
- Maluf-Filho F, Martins Bda C, de Lima MS, et al. Etiology, endoscopic management and mortality of upper gastrointestinal bleeding in patients with cancer. *United Eur Gastroenterol J*. 2013;1:60–67.
- Fontanella C, Ongaro E, Bolzonello S, et al. Clinical advances in the development of novel VEGFR2 inhibitors. *Ann Transl Med*. 2014;2:123.
- Peng L, Bu Z, Zhou Y, et al. Hemorrhagic events in cancer patients treated with aflibercept: a meta-analysis. *Tumour Biol*. 2014;35:9419–9427.
- Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. *Lancet Oncol*. 2009;10:559–568.
- Qi WX, Shen F, Qing Z, et al. Risk of gastrointestinal perforation in cancer patients treated with aflibercept: a systematic review and meta-analysis. *Tumour Biol*. 2014;35:10715–10722.
- Qi WX, Tang LN, Sun YJ, et al. Incidence and risk of hemorrhagic events with vascular endothelial growth factor receptor tyrosine-kinase inhibitors: an up-to-date meta-analysis of 27 randomized controlled trials. *Ann Oncol*. 2013;24:2943–2952.
- Qi WX, Sun YJ, Tang LN, et al. Risk of gastrointestinal perforation in cancer patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2014;89:394–403.
- Shirasaka T. Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. *Jpn J Clin Oncol*. 2009;39:2–15.
- Boku N, Yamamoto S, Fukuda H, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol*. 2009;10:1063–1069.
- Chen J, Shen W, Xia J, et al. Effect of S-1 maintenance chemotherapy following DCF regimen in patients with advanced gastric cancer. *Nan Fang Yi Ke Da Xue Xue Bao*. 2014;34:1057–1060.