

Case Report

Apatinib combined with S-1 in patients with advanced pancreatic cancer causing sudden massive hemorrhage: report of two cases

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Received November 1, 2017; Accepted March 23, 2018; Epub June 15, 2018; Published June 30, 2018

Abstract: Pancreatic cancer is the most malignant tumor of digestive system, and no effective treatment specifically for pancreatic cancer currently exists. Advanced pancreatic cancer chemotherapy, radiotherapy, and molecular targeted therapy might not be favorable and result in poor prognosis. Apatinib is currently being tested in patients with pancreatic or lung cancers. Here we report 2 cases using Apatinib and S-1 to treat advanced pancreatic cancer. Two patients had an adverse event involving sudden massive hemorrhage from the upper gastrointestinal tract and unfortunately died although after a timely rescue. Apatinib and gimeracil can cause gastrointestinal bleeding and may increase the risk of bleeding if combined with two drugs. We report these 2 cases with sudden massive hemorrhage with the objective of investigating the risk of anti-angiogenic drugs in patients with advanced pancreatic cancer. Furthermore, we provide reference for clinical rational drug use. In conclusion, suggestions on the clinical application of anti-angiogenic drugs should consider the risk of bleeding, especially in combination with chemotherapy.

Keywords: Advanced pancreatic cancer, VEGFR-2, Apatinib, S-1, adverse event

Introduction

Pancreatic cancer is the most malignant tumor of digestive system, and the incidence and mortality are increasing each year [1]. Although new treatments and drug updates for the treatment of pancreatic cancer patients has brought new hope, it is regrettable that the overall efficacy of advanced pancreatic cancer is far from satisfactory. The present shows that the median overall survival (mOS) with gemcitabine alone, gemcitabine plus erlotinib, and gemcitabine plus nab-paclitxel is only 6 to 9 months, although the new effective chemotherapy regimen FOLFIRINOX significantly improved the mOS but it is still < 1 year (11.3 months) [2]. Treatment of advanced pancreatic cancer has reached a bottleneck. Thus, more effective therapies are needed. In addition, all advances so far have been with the use of chemotherapy, molecularly targeted therapies are being tested in pancreatic cancer and may be able to further alter the natural history of this disease. The first-line therapy with locally advanced unresectable pancreatic adenocarcinoma with poor

performance status is gemcitabine, but recent data show that monotherapy with Tegafur, Gimeracil and Oteracil Potassium Capsules (S-1) demonstrated non-inferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer [3]. Therefore, S-1 is considered to be the first choice for the treatment of advanced pancreatic cancer in China [4]. Apatinib is a novel small molecule that may specifically bind vascular endothelial growth factor receptor-2 (VEGFR-2) shows good efficacy and safety in a variety of advanced solid tumors including gastric cancer, non-small cell lung cancer, breast cancer, and liver cancer clinical trials in China [5]. The latest research data further revealed that VEGFR-2 inhibitors combined with chemotherapy can significantly enhance the anti-tumor effect of chemotherapy drugs [6, 7].

In this study, 2 male patients with advanced pancreatic cancer received Apatinib (developed by Jiangsu Hengrui Medicine Co., Ltd., China) combined with S-1 (developed by Jiangsu Heng-

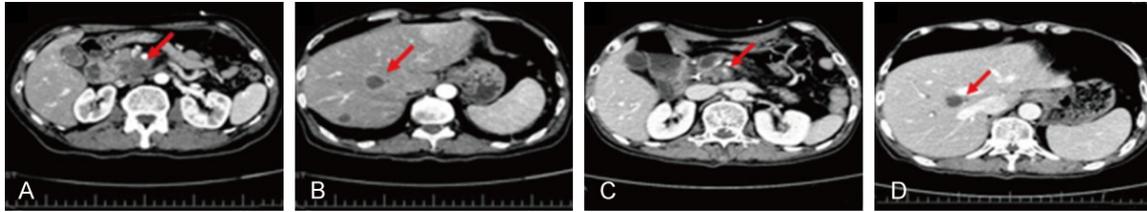


Figure 1. (A, B) Enhanced abdominal CT scan. On May 27, 2016, enhanced abdominal CT scan revealed the mass of the pancreatic head was 4.7×4.3 cm (A), and there were multiple metastases in the liver, the largest was about 1.9×1.7 cm (B). (C, D) Enhanced abdominal CT scan. On August 2, 2016, enhanced abdominal CT scan revealed the mass of the pancreatic head was reduced to 2.3×2.0 cm (C), the right anterior lobe of the liver metastases disappeared, the right posterior lobe of the liver was reduced to 1.7×1.5 cm (D).

rui Medicine Co. Ltd., China) when after provided written, informed consent. Unfortunately, these 2 patients had an adverse event involving sudden massive hemorrhage from the upper gastrointestinal tract resulting in death. We report these 2 cases with sudden massive hemorrhage to provide reference for the clinical application of anti-angiogenic drugs in advanced pancreatic cancer, especially in combination with chemotherapy. Furthermore, we hope that clinical workers pay more attention to adverse drug reactions and explore the possible causes of bleeding.

Written informed consent was obtained from the patient's closest relatives for publication of this case report and any accompanying images. This is a study involving human participants, but not a clinical trial. Investigations were conducted in accordance with the ethical standards and according to the Declaration of Helsinki and according to national and international guidelines and had been approved by the authors' institutional review board.

Case reports

Case 1

In May 2016, a 52-year-old male came to the hospital because of upper abdominal pain for 3 months. Physical examinations showed skin stained yellow sclera III, abdominal tenderness, without any signs of peritonitis. A computed tomography (CT) scan demonstrated that the mass of the pancreatic head was 4.7×4.3 (centimeters) (**Figure 1A**), and there were multiple metastases in the liver, the largest was about 1.9×1.7 (centimeters) (**Figure 1B**). This patient had an Eastern Cooperative Oncology Group (ECOG) score of 3 [8]. Laboratory testing,

including blood routine, biochemical, urinalysis, fecal occult blood test, and blood coagulation function, revealed some abnormal results total bilirubin (TBIL) $345.4 \mu\text{mol/L}$, direct bilirubin (DBIL) $311.2 \mu\text{mol/L}$, aspartate aminotransferase (ALT) 75 U/L , alanine aminotransferase (AST) 62 U/L . Tumor markers: carcinoembryonic antigen (CEA) 10.04 ng/mL , carbohydrate antigen-199 (CA-199) $> 1,000 \text{ U/mL}$, Carbohydrate antigen-125 (CA-125) $54.2 \mu\text{g/L}$. Based on the above examination, the patient was diagnosed with advanced pancreatic cancer with liver and lung metastasis and clinically staged as $\text{cT}_4\text{N}_1\text{M}_1$, stage IV (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science + Business Media, LLC (SBM).

In May 24, 2016, the percutaneous transhepatic cholangial drainage was performed because of the patient with jaundice and pruritus. In June 8, 2016, laboratory testing for liver function recovery showed TBIL 96.5 mol/L , DBIL 90.3 mol/L , ALT 39 U/L , and AST 32 U/L . After the patient provided written, informed consent, Apatinib (675 mg, orally administered once a day) combined with S-1 (50 mg, twice a day for 14 days followed by a 7 day rest) was then administered on June 8, 2016. Tumor evaluation was performed every 3 treatment cycles.

In August 2, 2016, CT scan demonstrated the size of pancreatic head mass was reduced to 2.3×2.0 (centimeters) (**Figure 1C**). The right anterior lobe of the liver metastases disappeared, the right posterior lobe of the liver was reduced to 1.7×1.5 (centimeters) (**Figure 1D**),

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Table 1. Changes in tumor markers before and after treatment

Date	May 23, 2016	Jun 20, 2016	Jul 12, 2016	Jul 20, 2016	Aug 2, 2016	Aug 10, 2016
CEA (ng/ml)	10.04	10.03	7.92	6.03	6.38	6.22
AFP (ng/ml)	3.78	1.97	< 1.80	< 1.80	< 1.80	< 1.80
CA125 (U/ml)	54.2	105.9	45.29	32.06	39.23	25.83
CA153 (U/ml)	6.97	6.52	4.42	3.51	3.79	2.92
CA199 (U/ml)	> 1,000	> 1,000	> 1,000	> 1,000	> 1,000	> 1,000
CA-50 (U/ml)	> 180.00	> 180.00	> 180.00	> 180.00	> 180.00	> 180.00

Note: CEA: carcinoembryonic antigen; CA: carbohydrate antigen; AFP: alpha-fetoprotein; <: lower than; >: more than.



Figure 2. Enhanced abdominal CT scan. October 14, 2016, enhanced abdominal CT scan revealed the lesions were located on the pancreatic tail (A) and metastases on the liver (B, C).

which was considered to be PR. Since taking the drugs, the tumor markers CEA, alpha-fetoprotein (AFP), CA-125, CA-153 were decreased, while CA-199 and CA-50 had no significant changes (Table 1).

Treatment-related side effects were monitored weekly during Apatinib treatment. The side effects included mild hand foot syndrome, 2 degree digestive tract reaction (mainly diarrhea), and the quality of life was significantly improved (ECOG from 3 to 1 points). However, in the morning of September 13, 2016, the patient had a sudden massive hemorrhage from the upper gastrointestinal tract. Although the patient received coagulation, rehydration, rescue, and other symptomatic treatment, the patient still died. In addition to fatal gastrointestinal bleeding, we did not observe any toxic effects such as high blood pressure, bone marrow suppression, cardiac toxicity, pulmonary toxicity, peripheral nerve toxicity, thrombosis, proteinuria, and so on.

Case 2

In September 29, 2016, a 49-year-old Chinese man visited hospital with more than half month history of upper abdominal persistent pain. This patient underwent blood routine, biochemical, urinalysis, fecal occult blood test, and blood coagulation function, electrolytes, elec-

trocardiogram and radiographic examination. Blood routine, liver, and kidney function, electrolytes and urine routine were normal, but the imaging examination showed (Figure 2) the pancreatic tail tumor about the size of 6.1 × 3.5 × 3.1 (centimeters), considering the pancreatic cancer, adjacent splenic vein in-

vasion and gastric varices. Liver segment II, III, VIII segment multiple nodules, large in the II section, the size of about 1.5 × 1.3 (centimeters), consider metastatic disease; hepatic portal lymph node enlargement, size of about 1.5 × 1.3 (centimeters); peritoneal effusion; portal vein right and splenic vein thrombosis. The diagnosis was pancreatic cancer with multiple metastases with AJCC cT₄N₁M₁, stage IV.

Inform patients and their families about the necessity of chemotherapy and targeted therapy, and the possible adverse reactions. After the patient provided written informed consent, Apatinib combined with S-1 was then administered from October 14, 2016. After 3 days of treatment, this patient had mild diarrhea and developed hiccups, so we gave him inhibit gastric acid secretion and promoted gastric motility and other symptomatic treatment. In November 4, 2016, this patient developed acute gastrointestinal bleeding (oral, nasal see a lot of blood outflow) resulting in death.

Discussion

Pancreatic cancer is associated with gastrointestinal bleeding and 2.6% of pancreatic cancer patients have the primary manifestation of gastrointestinal bleeding [9]. However, we report 2 death cases of advanced pancreatic cancer with upper digestive tract hemorrhage

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during the period of Apatinib and S-1 combined therapy, so we hypothesized that the bleeding event may be related to adverse drug reactions. Combined with the domestic and foreign literature, this paper further explored the possible factors of bleeding and to provide the reference for security of drug usage in clinical practice.

Apatinib causes platelet dysfunction and vascular endothelial cell tissue factor synthesis decrease and damage to the integrity of blood vessels leads to bleeding by specifically binding VEGFR-2 [10, 11]. Phase I clinical study of Apatinib treatment for advanced solid tumors was found to result in 23.9% patients experiencing bleeding, most of which were found at tumor sites. Grade 3 alimentary tract hemorrhage was noted in 1 patient, mostly attributed to tumor necrosis and active antiangiogenesis [12]. The bleeding symptoms include gastrointestinal bleeding, hematemesis, hemoptysis, fecal occult blood, urine occult blood, skin bleeding points, but no massive hemorrhage [13]. Therefore, anti-angiogenic drugs have the risk of bleeding caused by adverse reactions, clinicians should be prescribed carefully and more close clinical monitoring should be done when patients take it.

Additionally, the important clinically relevant finding was that S-1 may prevents bleeding [14]. A study showed that S-1 combined with gemcitabine chemotherapy can reduced duodenal infiltration of pancreatic cancer to achieve hemostasis [9]. However, some scholars have pointed out a strong relationship between S-1 and hemorrhage. A study of three-weekly S-1 monotherapy as first-line treatment in patients with metastatic gastric cancer found grade 3 gastrointestinal hemorrhage in one patient, whereas two patients died due to intracranial hemorrhage during treatment [15]. Another important finding was that treatment-related death caused by gastrointestinal bleeding occurred when S-1 and irinotecan plus bevacizumab for oxaliplatin-refractory metastatic colorectal cancer [16]. These findings suggest that patients should undergo continuous toxicity monitoring when receiving S-1 alone or in combination with other chemotherapeutic agents, especially with anti-angiogenic drugs.

As is known, the risk of bleeding should be considered for all patients when using anti-angiogenic drugs. The risks such as ulcerative type

gastric cancer, abnormal coagulation function, non steroidal anti-inflammatory drugs or using anticoagulant, and so on. For these patients, anti-angiogenic drugs should be used with caution to avoid increasing the risk of bleeding. In our 2 cases, we fully evaluated bleeding tendency and related symptoms before and during treatment, including the blood coagulation index, blood, urine and urine sediment quantitative analysis, the factors of fecal occult blood test, hematemesis or melena etc., but any risks of bleeding were not found. Therefore, these two patients were more likely to have a large vessel rupture.

At present, the reasons of serious bleeding to death and the probability about S-1 combined with Apatinib in the treatment of advanced pancreatic cancer, are not described in the literature. We speculate that there are some predisposing or synergistic factors in addition to adverse drug reactions, such as pancreatic special anatomical position, rapid tumor reduction, gastrointestinal bleeding etc. First, the rupture of esophageal or gastric varices secondary to obstruction of the splenic or portal vein, tumor hemorrhage from the pancreatic duct orifice, and bleeding due to direct infiltration of the tumor into the stomach or duodenum [17]. However, direct invasion to gastrointestinal tract by pancreatic adenocarcinoma, while rare, has been reported [18]. Previous studies evaluating pancreatic tumors usually have the character of the infiltrative growth, but seldom cause bleeding because of their ischemic nature [19]. One unanticipated finding was that once bleeding has occurred it will result in serious massive blood loss [9]. Herein, we report the second patient with splenic vein invasion, gastric varices, right portal vein and splenic vein thrombosis, which was more prone to the risk of bleeding. Second, the proliferation of tumor angiogenesis is prone to erosion and bleeding, and the rapid shrinkage of the tumor can cause bleeding. The first patient was found to have a primary lesion that narrowed and one of the liver metastases disappeared, and the levels of tumor markers (CEA, CA-125, etc.) were reduced, so this factor can't be excluded. In addition, the most interesting finding was that CA-199 may be a warning of gastrointestinal hemorrhage, particularly when it is > 1,000 U/m [20].

In conclusion, Apatinib combined with S-1 may increase the bleeding in the treatment of ad-

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vanced pancreatic cancer. Therefore, clinicians should closely monitor patients with possible adverse reactions, and improve the safety and effectiveness of drug therapy. Further studies are needed to confirm the efficacy and safety of Apatinib combined with S-1 in the clinical treatment of advanced pancreatic cancer.

Acknowledgements

This study was funded by Award Number Y-HR-2015-218 from the Beijing Xisike Clinical Oncology Research Foundation.

Disclosure of conflict of interest

None.

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