Extraordinary response of metastatic pancreatic cancer to apatinib after failed chemotherapy: A case report and literature review

Cheng-Ming Li, Zhi-Chao Liu, You-Ting Bao, Xin-Dong Sun, Lin-Lin Wang

Cheng-Ming Li, Zhi-Chao Liu, You-Ting Bao, Xin-Dong Sun, Lin-Lin Wang, Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan 250117, Shandong Province, China

Lin-Lin Wang, School of Medicine, Shandong University, Jinan 250012, Shandong Province, China

You-Ting Bao, Department of Oncology, Weifang Medical University, Weifang 261042, Shandong Province, China

ORCID number: Cheng-Ming Li (0000-0002-1111-3268); Zhi-Chao Liu (0000-0001-7313-2504); You-Ting Bao (0000-0001-6349-5125); Xin-Dong Sun (0000-0003-2325-1366); Lin-Lin Wang (0000-0002-2873-4204).

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Correspondence to: Lin-Lin Wang, MD, PhD, Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Jinan 250117, Shandong Province, China. 13793187739@163.com

Telephone: +86-531-67626142
Fax: +86-531-67626141

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Abstract
Chemotherapy has limited efficacy in the treatment of advanced and metastatic pancreatic cancer (PC), and has serious side effects. The development of novel effective agents, especially targeted therapy, is essential...
for patients with PC. We present a 58-year-old Chinese woman initially diagnosed with locally advanced PC. As the disease progressed to Stage IV, the patient was unable to tolerate chemotherapy after the fourth-line treatment. She was then treated with apatinib, a novel and highly selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor-2 and achieved a progression-free-survival of 7 mo. All drug-related side effects were well controlled with medication. To the best of our knowledge, this is the first case of PC which responded to apatinib. Considering this remarkable response, apatinib may be a promising agent in the treatment of PC. We also reviewed the literature on chemotherapy and targeted therapy, especially the anti-angiogenesis therapy for patients with PC, and investigated the effect of apatinib in other solid tumors as well.

Key words: Anti-angiogenesis; Apatinib; Pancreatic cancer; Targeted therapy; Vascular endothelial growth factor receptor-2

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Core tip: As chemotherapy has limited efficacy in the treatment of advanced and metastatic pancreatic cancer, targeted therapy is becoming increasingly important in patients with pancreatic cancer. The case reported herein suggests that apatinib, a novel and highly selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor-2, may be a promising and useful agent in the treatment of pancreatic cancer.

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INTRODUCTION

Pancreatic cancer (PC) is a malignant tumor with a poor prognosis, and is the seventh most common cancer worldwide[1]. Chemotherapy or chemoradiation are recommended as primary therapy according to the National Comprehensive Cancer Network (NCCN) guideline for advanced and metastatic PC[2]. However, the therapeutic outcomes are unsatisfactory, with 1-year survival rates of only 17%-23%[3-5]. Given that there is limited evidence that further systemic therapy provides meaningful benefit for patients who have progressed on chemotherapy, the development of novel effective agents, including targeted therapy, to improve patient outcome is required.

Tumor angiogenesis has been found to be essential in the proliferation, invasion and metastasis of PC[6-9]. Vascular endothelial growth factor receptor-2 (VEGFR-2) is a major element involved in pancreatic tumor angiogenesis[10-13]. Therefore, interference with the VEGF-2 signaling pathway may have therapeutic efficacy in the treatment of PC by preventing angiogenesis.

Apatinib (Hengrui Pharmaceutical Co., Ltd., Shanghai, China), also known as YN968D1, is a multiple kinase inhibitor with in vitro activity against VEGFR-2, PDGFR-beta, c-Kit, and c-src[14,15]. It was shown to have a survival benefit in gastric cancer in a Phase II[16] and III[17] trial and is currently being studied in multiple solid tumor types, such as colon and breast cancers[18-20]. Because of its easy administration, better compliance, reduced toxicity and improved outcomes, apatinib has demonstrated substantial potential as a new therapeutic option in a variety of tumor types[17,21].

Here, we report a patient with PC who was treated with apatinib following failure of the fourth-line therapy and achieved a progression-free survival (PFS) of 7 mo, demonstrating the potential of apatinib in the treatment of PC. To the best of our knowledge, this is the first case of PC which responded to apatinib.

CASE REPORT

In November 2014, a 58-year-old woman attended our hospital complaining of persistent pain in the upper abdomen and back, following dyspepsia for approximately 4 d. Physical examination suggested tenderness in the upper abdomen but without rebound pain. The serum carbohydrate antigen 19-9 (CA19-9) level was 148 U/mL (normal range, 0-39 U/mL). An upper abdominal contrast-enhanced computed tomography (CT) scan revealed a 3.1 cm × 1.7 cm mass at the body of the pancreas (Figure 1A), with the mass having an intimate connection to the splenic artery and vein. An enlarged lymph node was detected behind the aorta abdominals (Figure 1B). An $^{18}$F-FDG positron emission tomography (PET) scan also displayed a mass in the body of the pancreas with an SUV of 6.2 and an enlarged lymph node with an SUV of 4.8 (Figure 1C and D). Subsequently, an endoscopic biopsy of the mass showed a moderately differentiated adenocarcinoma (Figure 2). The patient was diagnosed with locally advanced, unresectable PC (cT4N1M0, Stage III).

Concurrent chemoradiotherapy (CCRT) with gemcitabine (GEM) weekly and 30 fractions of radiotherapy were administered from November 7 to December 18, 2014. When CCRT was completed, the tumor response was considered stable disease (SD) on a repeat abdominal CT according to the modified
Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The CA19-9 level gradually decreased to 125.6 U/mL. GEM with oxaliplatin was then administered for 4 cycles. An abdominal CT scan revealed a partial response, while serum CA19-9 level gradually decreased to a normal value (24.4 U/mL). The timeline of treatment and trend in CA19-9 during treatment are displayed in Figure 3.

However, 1 mo later, the patient attended our hospital again because of recurrence of upper abdominal pain. The CT scan showed metastatic lesions in the right pleura and lungs (Figure 4A-D), while the lesion in the pancreas and enlarged lymph node remained stable (Figure 4E and F). Clinical restaging showed cT4N1M1, Stage IV. The CA19-9 level increased to 150.8 U/mL. From June 27, 2015, 4 cycles of paclitaxel-albumin with S-1 were administered. The response after 2 courses and 4 courses was SD. The CA19-9 level gradually decreased to 46.87 U/mL, which was almost a normal value (Figure 3).

Approximately 4 mo later, a CT scan showed that the primary as well as the metastatic lesions had progressed. The CA19-9 level was 107.6 U/mL. As the patient had good performance status (PS), the fourth-line therapy with FOLFOX4 was administered. After 3 cycles, the CT scan showed that response to treatment was SD. However, the CA19-9 level had gradually increased from 107.6 U/mL to 302.3 U/mL. The patient was unable to tolerate this regimen due to gastrointestinal toxicity, and refused further chemotherapy. From June 3, 2016, the patient received apatinib (500 mg p.o. qd) as the fifth-line treatment. The CA19-9 level after 15 d of apatinib treatment decreased sharply from 302.3 U/mL to 88.8 U/mL. The CA19-9 level was tested every 2 wk and a CT scan was performed every 8 wk during the follow-up. The CA19-9 level was maintained between 56.8 U/mL and 92.4 U/mL (Figure 3) and the primary mass decreased from 1.7 cm to 1.2 cm, and then to 1.0 cm (Figure 5D-F) while other lesions showed no obvious

Figure 1  Abdominal CT and ¹⁸F-FDG PET/CT show lesions located in the pancreas and behind the aorta abdominalis. A: A 3.1 cm × 1.7 cm mass at the body of the pancreas; B: An enlarged lymph node behind the aorta abdominalis; C: The mass in the body of the pancreas with an SUV of 6.2; D: The enlarged lymph node with an SUV of 4.8. CT: Computed tomography; PET: Positron emission tomography.

Figure 2  Hematoxylin and eosin staining of a tumor section (× 200). The pathological diagnosis was moderately differentiated adenocarcinoma.
tumor response was SD but the CA19-9 level gradually increased. Due to chemotherapy intolerance, apatinib was then given as the fifth-line therapy to this patient. PFS following apatinib therapy was 7 mo. In addition, the patient tolerated apatinib well, with satisfactory quality of life.

With current chemotherapy regimens for PC, including GEM, paclitaxel-albumin, S-1, oxaliplatin, 5-FU, leucovorin and irinotecan, the median survival for patients with unresectable or metastatic PC is 9-11 mo\(^4,22,23\). In recent years, an increasing number of targeted drugs for PC have been studied. Erlotinib is the only targeted drug approved by the Federal Drug Administration to treat PC. In a randomized Phase III trial\(^3\), the median survival and 1-year survival rate both increased in patients treated with GEM plus erlotinib, compared to those treated with only GEM. Although these results seem positive, the median overall survival (OS) was only prolonged by 9.9 d (6.24 mo vs 5.91 mo, \(P = 0.038\)) and the objective response rates (ORR) were not significantly different between the two treatment arms (57.5% vs 49.2%, \(P = 0.07\)). Furthermore, a higher incidence of some adverse events was observed with erlotinib plus GEM. In a small-sample study, sorafenib plus erlotinib also did not improve either survival or PFS rate as compared to a historical control\(^24\). The ViP trial, a Phase II double-blind, multicenter, randomized placebo-controlled trial, showed that vandetanib combined with GEM in patients with advanced PC did not improve OS (8.83 mo vs 8.95 mo, \(P = 0.303\))\(^25\). In addition, a meta-analysis showed that there was no statistically significant improvement in survival when PC patients change (Figure 5A-C, G-I). The response to treatment with apatinib was SD.

On January 13, 2017, the patient attended our hospital complaining of difficulty in breathing and the recurrence of upper abdominal pain, a CT scan revealed several metastatic lesions in the liver and pleural effusion (Figure 6). In addition, the CA19-9 level had markedly increased to 1978.0 U/mL. Her PS diminished rapidly with a score of 3, and the disease had progressed. The patient finally died of multiple organ dysfunction resulting from pulmonary infection.

During apatinib treatment, this patient developed the primary side effects of hypertension (grade 2), dental ulcer (grade 2) and a higher serum alanine transaminase level (grade 1) according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 criteria. All side effects were well controlled with drug treatment and she had a PS score of 2.

This study was approved by the Institutional Review Board of Shandong Cancer Hospital Affiliated to Shandong University. The husband of the patient provided written informed consent.

**DISCUSSION**

To date, there has been no effective therapy for improving the survival of a PC patient due to its aggressive nature. In this case, we administered CCRT as first-line therapy and the tumor response was SD. GEM and oxaliplatin were administered as second-line therapy and PFS was only 3 mo. Paclitaxel-albumin with S-1 was then administered as third-line therapy and FOLFOX4 regimen as the fourth-line therapy. The tumor response was SD but the CA19-9 level gradually increased. Due to chemotherapy intolerance, apatinib was then given as the fifth-line therapy to this patient. PFS following apatinib therapy was 7 mo. In addition, the patient tolerated apatinib well, with satisfactory quality of life.

With current chemotherapy regimens for PC, including GEM, paclitaxel-albumin, S-1, oxaliplatin, 5-FU, leucovorin and irinotecan, the median survival for patients with unresectable or metastatic PC is 9-11 mo\(^4,22,23\). In recent years, an increasing number of targeted drugs for PC have been studied. Erlotinib is the only targeted drug approved by the Federal Drug Administration to treat PC. In a randomized Phase III trial\(^3\), the median survival and 1-year survival rate both increased in patients treated with GEM plus erlotinib, compared to those treated with only GEM. Although these results seem positive, the median overall survival (OS) was only prolonged by 9.9 d (6.24 mo vs 5.91 mo, \(P = 0.038\)) and the objective response rates (ORR) were not significantly different between the two treatment arms (57.5% vs 49.2%, \(P = 0.07\)). Furthermore, a higher incidence of some adverse events was observed with erlotinib plus GEM. In a small-sample study, sorafenib plus erlotinib also did not improve either survival or PFS rate as compared to a historical control\(^24\). The ViP trial, a Phase II double-blind, multicenter, randomized placebo-controlled trial, showed that vandetanib combined with GEM in patients with advanced PC did not improve OS (8.83 mo vs 8.95 mo, \(P = 0.303\))\(^25\). In addition, a meta-analysis showed that there was no statistically significant improvement in survival when PC patients
Figure 4 Computed tomography scan showed that the disease had progressed to stage IV. Metastatic lesions in the right pleura and lungs (lung window A, B; mediastinal window C, D). The lesion in the pancreas and enlarged lymph node remained stable (E, F).

Table 1 Clinical trials using targeted agents for advanced or metastatic pancreatic cancer

| Target medicine                       | Mechanism       | Phase | Stage                  | n  | Arm                                                      | PFS, mo | OS, mo | ORR      |
|---------------------------------------|-----------------|-------|------------------------|----|---------------------------------------------------------|--------|--------|----------|
| Cetuximab[27]                         | EGFR            | III   | Locally advanced/ metastatic | 746| A: GEM + cetuximab                                       | 3.4 vs 3.0 | 6.3 vs 5.9 | 49% vs 44% |
|                                       |                 |       |                        |    | B: GEM                                                  |        |        |          |
| Nimotuzumab[28]                        | EGFR            | III   | Locally advanced/ metastatic | 18 | GEM + nimotuzumab                                       | 3.71 vs 3.7 | 9.29 vs 9.29 | 55.50% |
| Lapatinib[29]                          | EGFR + Her-2    | II    | Metastatic             | 17 | Lapatinib + capecitabine                                | 2.6 vs 2.6 | 5.2 vs 5.2 | -        |
| Cixutumumab[30]                        | IGF-1R          | I b/ II | Metastatic             | 116| A: Erlotinib + cixutumumab + GEM                        | 3.6 vs 3.6 | 7.0 vs 6.7 | 12.28% vs 12.28% |
|                                       |                 |       |                        |    | B: Erlotinib + GEM                                     |        |        |          |
| Cetuximab + Everolimus[31]             | EGFR + mTOR     | II    | Locally advanced/ metastatic | 31 | Everolimus+ cetuximab + capcitabine                    | -      | 5.0    | 22.60%   |
| Cetuximab + trastuzumab[30]            | EGFR + Her-2    | I - II | Metastatic             | 33 | Cetuximab + trastuzumab                                | 1.8 vs 1.8 | 4.6 vs 4.6 | -        |
| Erlotinib + Selumetinib[32]            | EGFR + MEK1/2   | II    | Locally advanced/ metastatic | 46 | Erlotinib + selumetinib                                | 1.9 vs 1.9 | 7.3 vs 7.3 | -        |

EGFR: Epidermal growth factor receptor; GEM: Gemcitabine; ORR: Objective response rate.
were treated with erlotinib or cetuximab\cite{26}. Other trials where one\cite{27-30} or a combination of two targeted agents\cite{31-33} were administered for advanced or metastatic PC also did not show significant positive results (Table 1).

Angiogenesis is an essential and significant step in tumor growth as it supplies necessary oxygen, growth factors and nutrients, and is generally considered an attractive target in cancer therapy\cite{34-37}. Some studies have confirmed that PC is indeed angiogenesis-dependent\cite{6-9}. Bevacizumab, an anti-angiogenesis agent, is currently the most frequently studied drug for PC in clinical trials. A double-blind phase III trial of bevacizumab in combination with GEM and erlotinib for metastatic PC showed that the addition of bevacizumab led to a statistically significant

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Figure 5  The primary mass in the pancreas shrunk gradually during apatinib treatment: (D) 1.7 cm (E) 1.2 cm (F) 1.0 cm. The metastatic lesions showed no obvious change (A-C; G-I).

Figure 6  Disease progression. CT scan revealed several metastatic lesions in the liver (A) and pleural effusion (B). CT: Computed tomography.
improvement in PFS ($P = 0.0002$). However, there was no significant improvement in OS (7.1 mo vs 6.0 mo, $P = 0.2087$)\cite{38}. Moreover, in the CALGB 80303 trial\cite{39}, median PFS and ORR were similar in the two treatment arms (for PFS, 3.8 mo vs 2.9 mo, $P = 0.07$; for ORR, 13% vs 10%, respectively). However, in the subgroup analysis, the median survival was 7.9 mo in PS 0 patients, 4.8 mo in PS 1 patients and only 2.4 mo in PS 2 patients. These findings suggested that bevacizumab is much more effective in PS 0 and 1 patients. In another Phase II study\cite{40} of bevacizumab combined with chemotherapy, median PFS was 5.9 mo and median OS was 7.4 mo. Partial response and stable disease occurred in 30% and 45% of patients, respectively, which met the study’s primary endpoint. These studies\cite{39-41} demonstrated that further efforts should be focused on identifying subsets of PC patients who are more likely to benefit from bevacizumab. These findings indicate that anti-angiogenesis treatment has great potential in PC.

Tumors produce various angiogenic factors and cytokines to induce angiogenesis, which is essential for tumor growth. Among these tumor-derived factors, the VEGF family including VEGF-A to -D was initially identified as endothelial cell-specific mitogens with the ability to induce physiologic and pathologic angiogenesis\cite{42-46}. It has been reported that VEGF displays these broad vascular functions by the binding and activation of VEGF\cite{46-49}, especially VEGFR-2\cite{50-52}, mainly expressed in vascular endothelial cells. As described in Figure 7, bevacizumab, a humanized monoclonal antibody that only targets VEGF-A to prevent its interaction with VEGFR-2, was the first targeted antiangiogenic agent approved for use in oncology\cite{53}. Apatinib, the first generation of oral anti-angiogenesis drugs, mainly targets VEGFR-2 through the intracellular ATP-binding site that inhibits all VEGF-stimulated endothelial cell migration and proliferation, decreases tumor microvascular density and promotes apoptosis\cite{11,54,55}. Therefore, it seems that apatinib may have more potential in anti-angiogenesis than bevacizumab by affecting the VEGFR-2 pathway of angiogenesis.

Apatinib shows antitumor efficacy and good tolerance in mice when administered alone or in combination with chemotherapeutic drugs against a broad range of human tumor xenografts\cite{15}. In patients with advanced gastric or gastroesophageal junction adenocarcinoma, a Phase II study\cite{16} and a Phase III study\cite{20} showed that both OS and median PFS were significantly improved in the apatinib group. Furthermore, other clinical trials\cite{17,56} concluded that apatinib has substantial clinical activity without significant additional toxicity in patients with advanced
non-squamous and non-small cell lung cancer and hepatocellular carcinoma. Whether apatinib has an important role in the treatment of PC is unknown.

The reason for the use of apatinib in our case were unsatisfactory treatment efficacy after the fourth-line chemotherapy, but the patient still wished to continue the treatment. According to the general condition of the patient who had a PS 2, she was treated with apatinib at a daily dose of 500 mg. After 15 d of apatinib treatment, the CA19-9 level decreased sharply from 302.3 U/mL to 88.8 U/mL. Following a period of treatment, the primary mass was reduced in size and other metastatic diseases were well controlled for 7 mo. Although this is an individual case, apatinib did demonstrate its curative effect in PC. As an anti-angiogenesis therapy, it seems that apatinib may be effective in the treatment of PC.

Here, we report the first case of PC which responded to apatinib. It seems that apatinib may provide an additional option for the targeted treatment of PC. Nevertheless, further large-scale prospective studies on apatinib are required to verify its efficacy in the treatment of PC.

COMMENTS

Case characteristics
A 58-year-old woman with no significant medical history attended our hospital complaining of persistent pain in the upper abdomen and back, following dyspepsia for approximately 4 d.

Clinical diagnosis
Physical examination suggested tenderness in her upper abdomen but without rebound pain.

Differential diagnosis
Pancreatitis, pancreatic neuroendocrine tumor, cholecystitis, ampullary carcinoma.

Laboratory diagnosis
The serum carbohydrate antigen 19-9 level was 148 U/mL when diagnosed.

Imaging diagnosis
Computed tomography revealed a 3.1 cm × 1.7 cm mass at the body of the pancreas, and an enlarged lymph node was detected behind the aorta abdominals. 18F-FDG positron emission tomography displayed a mass in the body of the pancreas with an SUV of 6.2 and an enlarged lymph node with an SUV of 4.8.

Pathological diagnosis
Moderately differentiated adenocarcinoma.

Treatment
Chemotherapy, radiotherapy, and targeted therapy.

Related reports
Recently, many targeted drugs for pancreatic cancer have been studied. Erlotinib is the only targeted drug approved by the Federal Drug Administration to treat pancreatic cancer. Apatinib, the first generation of oral anti-angiogenesis drugs, mainly targets vascular endothelial growth factor receptor-2 (VEGFR-2). In patients with advanced gastric or gastroesophageal junction adenocarcinoma, a Phase II study and a Phase III study showed that both overall survival and median progression-free survival were significantly improved in the apatinib group. Furthermore, other clinical trials concluded that apatinib has substantial clinical activity without significant additional toxicity in patients with advanced non-squamous and non-small cell lung cancer and hepatocellular carcinoma. Therefore, apatinib seems have potential in anti-angiogenesis by affecting the VEGFR-2 pathway of angiogenesis.

Term explanation
Apatinib, also known as YN968D1, is a multiple kinase inhibitor with in vitro activity against VEGFR-2, PDGFR-beta, c-Kit, and c-src.

Experiences and lessons
Apatinib may provide an additional option for the targeted treatment of pancreatic cancer, and further large-scale prospective studies on apatinib are required to verify its efficacy in the treatment of pancreatic cancer.

Peer-review
In this study, it showed that apatinib, a first-generation anti-angiogenesis drug targeting VEGFR-2, indeed improved the life of a patient with metastatic pancreatic cancer.

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