Original Research Article

Clinical efficacy of apatinib as a second-line treatment for advanced pancreatic cancer in a Chinese tertiary cancer health facility

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Abstract

Purpose: To study the effectiveness and safety of apatinib as second-line treatment for advanced pancreatic cancer (APC) in a Chinese tertiary cancer hospital.

Methods: Two groups of APC patients who received treatment with single-agent or two-drug combination of gemcitabine-based first-line therapy (50 per group) in The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing were assessed. The study group received apatinib at or above the second line treatment, while the control group was treated with second-line chemotherapy, which was different from first-line single-drug chemotherapy. Patients received treatments until there was improvement in their conditions, or until adverse reactions became intolerable. Complete remission (CR), partial remission (PR), disease stabilization (SD), disease progression (PD), incidence of adverse reactions, and progression-free survival (PFS) of the patients were recorded.

Results: The number of PR cases in APC patients who received apatinib as second-line therapy, and the number of PD patients were higher than the corresponding populations in the control group ($p < 0.05$). Treatment effectiveness was significantly higher in study group patients than in control subjects ($p < 0.05$). However, the incidence of adverse reactions was lower in the study group than in control group. Median PFS in the study group (5 months) was significantly higher than that of the control group (4.1 months, $p < 0.05$).

Conclusion: The clinical efficacy of apatinib as second-line treatment for advanced pancreatic cancer is higher than that of the single drug. Apatinib is associated with low incidence of adverse reactions which prolongs PFS. Thus, apatinib has potentials for the clinical management of pancreatic cancer.

Keywords: Apatinib, Pancreatic cancer, Partial remission, Progression-free survival

INTRODUCTION

Pancreatic cancer is one of the most malignant tumors of the digestive system. In recent years, there has been an upsurge in the incidence of pancreatic cancer. Current statistics from the China Cancer Center reveal that pancreatic cancer ranks 8th in the incidence of male malignant tumors in Chinese cities, and 5th in the mortality rate of malignant tumors in Beijing and Shanghai [1-3]. When the tumor undergoes

metastasis and invades adjacent blood vessels and distant tissues, less than 20 % of the affected patients are eligible for surgical resection. Moreover, even after surgical resection, recurrence is as high as 80 %, which reduces the five-year survival of pancreatic cancer patients below 5 % [4].

Postoperative poor prognosis and high recurrence suggest the necessity for combination of chemotherapy and radiotherapy in the treatment of pancreatic cancer. However, current adjuvant and neoadjuvant therapy are not effective against pancreatic cancer.

Oncogene expression caused by multiple mutations or the inactivation of tumor suppressor genes and resistance to apoptosis are important mechanisms of drug resistance in pancreatic cancer [5-7]. Moreover, gemcitabine-based first-line chemotherapy is not effective enough. Thus, there is a need to evolve more effective second-line chemotherapy to improve the prognosis of advanced pancreatic cancer.

Apatinib mesylate is a small, novel and oral targeted drug developed in China. It exerts potent anti-tumor angiogenic properties. Apatinib exerts anti-tumor effects when administered alone. Studies have found that apatinib has a broad-spectrum anti-tumor effects. It exerts anticancer effects against gastric, lung, colon, breast, and liver cancers. Gemcitabine and apatinib do not have cross-resistance. Therefore, it is important to carry out clinical study of late pancreatic cancer in which second-line treatment of gemcitabine is ineffective.

The present study investigated 50 pancreatic cancer patients who underwent second-line therapy with apatinib, and 50 other patients who used a single drug different from the first-line regimen for second-line therapy, with respect to prognosis, efficacy and adverse reactions. The significance of apatinib in the treatment of pancreatic cancer was investigated.

METHODS

Clinical profile of patients

There were 50 advanced pancreatic cancer patients from The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, in the study group. The patients who were unresponsive, or relapsed after single or combined first-line treatment with gemcitabine were enrolled from January 2016 to January 2018. Apatinib was used for second-line treatment. The subjects comprised 28 men and 22 women of ages 30 -

75 years. There were 28 cases of carcinoma of head of pancreas, 12 cases of carcinoma of body of pancreas, and 10 cases of carcinoma of tail of pancreas.

Control group comprised 50 patients with APC who received gemcitabine-based monotherapy or combination of two first-line treatment drugs, or who relapsed, from January 2018 to January 2019, or patients treated with a single drug different from the first-line regimen for second-line treatment. They were made up of 30 males and 20 females aged 32 - 78 y (mean age = 57.3 ± 10.5 y). There were 25 subjects with pancreatic head cancer, 14 patients with pancreatic body cancer, and 11 patients with pancreatic tail cancer.

This research was registered in Chinese Clinical Trial Registry (registration no. ChiCTR1800016762) and received approval from the Ethical Committee of Oncology Department of The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing (approval no. 201816301). It was carried out in line with the guidelines Helsinki declaration [8].

Inclusion and exclusion criteria

Inclusion criteria

Patients with single-agent or two-drug-based combination therapy with gemcitabine, who received continuous treatment with apatinib and other monotherapy, and patients whose disease treatment could be successfully followed up; patients whose CT examination results showed at least one measurable lesion; and patients who voluntarily enrolled and signed informed consent.

Exclusion criteria

Patients with other major organ diseases such as heart, liver and kidney; pancreatic cancer patients who had other tumors; and pregnant or lactating women.

Chemotherapy regimen

This comprised gemcitabine single-agent chemotherapy (1000 mg/m^2 day, 3 times a week for 8 weeks; oral teggio monotherapy (40 mg/m^2, 2 times a day for 28 days, 14 days for one course of treatment), and oral apatinib single-agent chemotherapy (oral apatinib 500 - 750 mg, depending on patient's body surface area and tolerance) once a day continuously until disease progression or occurrence of intolerable adverse reactions.

Evaluation of efficacy

After 2 cycles of treatment, CT was reviewed and the efficacy was evaluated according to the solid tumor remission assessment criteria (RECIST criteria). To qualify for *complete remission (CR),* all lesions would have been eliminated, without formation of new lesions. *Partial remission (PR)* implied that the sum of the maximum diameters (SMD) of lesions was decreased by $\geq$ 30 %, while *stable disease (SD)* meant that the SMD of the lesion was decreased by < 30 %, or increased by < 20%. *Disease progression (PD)* implied that the sum of the maximum diameter of the lesion was increased by $\geq$ 20%, or that new lesions appeared. *Objective effectiveness (ORR)* was calculated using Eq 1.

ORR (%) = [(CR + PR)/total cases × 100 … (1)

Progression-free survival (PFS) was recorded for each patient.

Statistical analysis

Data were statistically processed with SPSS 20.0 software package. Survival rate and median survival time were calculated using Kaplan-Meier method. No progression survival curves were drawn. Analysis of two different treatment options affecting PFS was done with Log-rank test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Efficacy

No CR cases were seen in the study and control groups. The control group had 12 cases of PR (24 %), 27 cases of SD (22 %), and 27 cases of PD (54 %). The ORR of the control group was 24 %. In the study group, there were 23 patients with PR (46 %), 15 patients with SD (30 %), and 12 patients with PD (24 %). The ORR of the study group was 46 % ($p < 0.05$). These results are shown in Table 1.

Adverse reactions

The incidence of adverse reactions and incidence of neutropenia were markedly fewer in the observation patients than in control patients ($p < 0.05$).

Table 3 shows disease progression-free survival of the two groups of patients. The progression-free survival of the study group at 5 and 15 months was markedly higher than that of control patients ($p < 0.05$). However, progression-free survival at 10 and 20 months were comparable in both groups ($p > 0.05$).

Table 1: Efficacy of the applied treatment

Group	CR	PR	SD	PD	ORR
Control	0(0%)	12(24%)	11(22%)	27(54%)	24%
Study	0(0%)	23(46%)	15(30%)	12(24%)	46%
P-value	1.0000	0.0353	0.4945	0.0038	0.0018

Table 2: Adverse reactions of patients

Adverse reaction	Control group	Study group	χ^2	*P*-value
Leukopenia	2(4%)	0(0%)	2.041	0.1531
Thrombocytopenia	8(16%)	3(6%)	2.554	0.1100
Neutropenia	8(16%)	2(4%)	4.000	0.0455
Diarrhea	3(6%)	2(4%)	0.211	0.6464
Nausea and vomiting	7(14%)	4(8%)	0.919	0.3377
Weak	3(6%)	1(2%)	1.042	0.3074
Liver and kidney damage	3(6%)	2(4%)	0.211	0.6464

Table 3: Progression-free survival of the patients [*n* (%)]

Group	*n*	5 months	10 months	15 months	20 months
Control	50	25(50)	16(32)	13(26)	5(10)
Study	50	14(28)	7(14)	4(8)	0(0)
P-value	-	0.0397	0.056	0.031	0.056

Disease progression-free survival (PFS) curve and log-rank test

The PFS curves of the two groups were drawn (Figure 1 and Table 4). The median PFS of observation and control patients were 5 months (95% CI: 4.6 - 7.4) and 4.1 months (95% CI: 3.4 - 4.6), respectively. The log-rank test of the progression-free survival curve of the two groups was $p = 0.000 < 0.05$, and the difference was statistically significant.
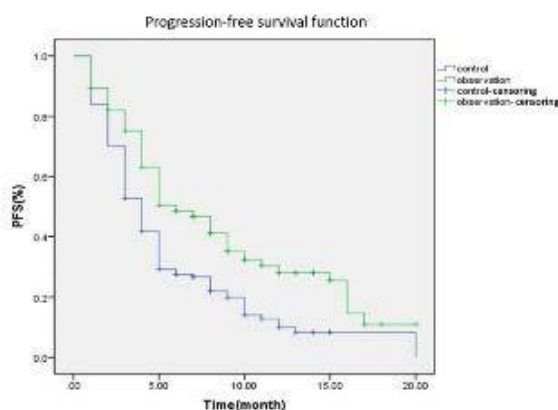

Figure 1: Progression-free survival function curves of patients in the two groups

Table 4: Survival curve log-rank analysis results

Parameter	χ^2	Df	Sig.
Log-Rank	19.154	1	0.000

DISCUSSION

Apatinib is a small VEGFR-2 tyrosine kinase inhibitor that inhibits tumor angiogenesis. Animal studies have shown that apatinib significantly inhibits tumor growth in a variety of mouse tumor models. Its mechanism of action involves competitive binding to the intracellular tyrosine ATP binding site of the receptor. This binding specifically inhibits VEGFR-2 tyrosine kinase activity, and blocks signal transduction after VEGF binding, thereby inhibiting tumor angiogenesis [9,10]. It is known that VEGF signaling is the most important regulator of angiogenesis [11]. The biological effects of apatinib against angiogenesis in tumor growth inhibition are expected to attract a lot of research interest with respect to treatment of pancreatic cancer.

It is known that VEGF promotes vascular survival by binding to VEGFR2 and inducing activation of downstream molecules of VEGFR2. It regulates several functions in vascular endothelial cells, including permeability and survival, and it is of primary importance in the survival of blood vessels. Studies have found that in many malignant tumors, over-expressions of VEGF and VEGFR are associated with accelerated tumor production, increased microvascular density, increased invasion, and poor prognosis [12]. Therefore, anti-angiogenic therapy is a promising therapeutic strategy in clinical practice.

It has been reported that cellular autocrine VEGF regulates the proliferation of VEGF-induced extrahepatic bile duct cancer (EBDC) [13]. Apatinib-induced blockage of the VEGF/VEGFR2 signaling pathway resulted in marked inhibition of the proliferative capacity of EBDC cells [14]. In another study, apatinib effectively induced apoptosis and inhibited the proliferation of intrahepatic cholangiocarcinoma cells through inhibition of the VEGF/VEGFR2/P13K/AKT signaling pathway [14].

In clinical trials on gastric cancer and non-small cell lung cancer (NSCLC), apatinib has shown good survival benefits and high safety, and it appreciably enhanced the prognosis of gastric cancer and breast cancer patients [9,15-17]. In a clinical study, it was found that apatinib prolonged the PFS of patients with advanced NSCLC [18]. Recently published studies showed that apatinib decreased the risk of death by almost 40 % in subjects with advanced or metastatic chemotherapy-refractory stage III gastric cancer and second-line treatment failure. Some investigators reported that apatinib enhanced the prognosis of cancer patients and produced some therapeutic effects on a variety of cancers [17-20]. However, not much research has been carried out on the use of apatinib for the treatment of pancreatic cancer.

At present, the main first-line drug for clinical treatment of pancreatic cancer is gemcitabine. However, some patients may not tolerate chemotherapy due to its obvious side effects. Therefore, some doctors have turned their attention to second-line drugs for patients with poor or unsatisfactory treatment outcomes with first-line chemotherapy drugs [21]. Apatinib was approved in 2014 for second-line treatment of gastric adenocarcinoma and gastroesophageal junction cancer [22,23]. The present study compared the clinical results of single-agent apatinib and single-agent, second-line chemotherapy treatments for advanced pancreatic cancer, so as to evaluate the clinical efficacy, safety and prognosis of apatinib for pancreatic cancer treatment. The results showed higher PR and SD values, and lower PD in study subjects than in controls. Moreover, incidence of adverse reactions such as leukopenia, thrombocytopenia, neutropenia,

diarrhea, vomiting, fatigue and liver and kidney injury were lower than in the study group.

These findings indicate that apatinib is effective as a second-line drug for the treatment of pancreatic cancer. Its clinical efficacy was better than that of gemcitabine and other single drugs, and the safety was also high. The longer the median PFS, the better the prognosis of patients. The median PFS in study patients was 0.4 months higher than that in control patients, although the increase was not obvious. The two PFS curves showed a non-parallel downward trend, and the PFS curve was always higher in the study patients who also had better prognosis of survival, relative to control. Results from Log-rank test revealed that apatinib as a second-line drug improved the prognosis of patients with advanced pancreatic cancer and prolonged their PFS.

Limitations of this study

The number of samples used in this study was relatively small. Therefore, there is need for a prospective, multicenter, randomized and controlled trial for confirmation of the reliability of the conclusions reached in this investigation.

CONCLUSION

The findings of this work suggest that apatinib prolongs PFS in patients with advanced pancreatic cancer who are unresponsive to first-line chemotherapy with gemcitabine-based regimen, and that its efficacy and safety are superior to those of other chemotherapy drugs. Thus, apatinib has a potential for clinical application in the treatment of pancreatic cancer.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Yan Zhang conceived and designed the study, Ning Sun, Chenchen Li, Yun Zhou, Lei Xia, Xiaoming Wang, Dongfeng Wang, Renhong Guo, Yan Zhang collected and analysed the data, while Ning Sun wrote the manuscript.

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