Anlotinib plus nab-paclitaxel/gemcitabine as first-line treatment prolongs survival in patients with unresectable or metastatic pancreatic adenocarcinoma: a retrospective cohort

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Background: The timely addition of anlotinib to the nab-paclitaxel/gemcitabine regimen may further increase the treatment efficacy for pancreatic adenocarcinoma (PDAC), which has not yet been reported. Therefore, we aimed to compare the efficacy and safety of anlotinib plus nab-paclitaxel/gemcitabine in the first-line treatment of patients with unresectable or metastatic PDAC.

Methods: This was a retrospective cohort of patients with unresectable or metastatic PDAC performed in The First Affiliated Hospital of Anhui Medical University from August 17, 2019 to April 3, 2021. Patients who received anlotinib plus nab-paclitaxel/gemcitabine treatment were defined as the anlotinib plus chemotherapy group and patients who received nab-paclitaxel/gemcitabine were defined as the chemotherapy group. The primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary outcomes were the objective response rate (ORR), the disease control rate (DCR), and toxic side effects. Clinical data and follow-up information were mainly obtained from hospital records or by telephone.

Results: A total of 33 patients were included in this study, with 17 cases in the anlotinib plus chemotherapy group and 16 cases in the chemotherapy group. The median PFS (mPFS) of the anlotinib plus chemotherapy group was 5 months while the mPFS of the chemotherapy group was 2.7 months (P=0.0220). The median OS (mOS) of the anlotinib plus chemotherapy group was 9 months while the mOS of the chemotherapy group was 6 months (P=0.0060). The 3-month and 6-month PFS, and the 6- and 12-month OS of the anlotinib plus chemotherapy group were significantly higher than those of the chemotherapy group (P<0.05). The proportion of patients with hematological toxicities in the anlotinib plus chemotherapy group was not significantly higher than that in the chemotherapy group.

Conclusions: Anlotinib plus nab-paclitaxel/gemcitabine as a first-line treatment regimen is safe and may prolong survival compared with nab-paclitaxel/gemcitabine chemotherapy in patients with unresectable or metastatic PDAC. Randomized controlled trials with large sample sizes are warranted to further evaluate the treatment effects of anlotinib in PDAC.

Keywords: Pancreatic adenocarcinoma (PDAC); anlotinib; nab-paclitaxel/gemcitabine; progression-free survival (PFS); overall survival (OS)

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Introduction

Pancreatic adenocarcinoma (PDAC) is the seventh leading cause of cancer death worldwide. According to the 2020 global cancer statistics, PDAC accounted for accounted for 496,000 new cases and roughly 466,000 deaths because of its poor prognosis (1). A total of 60% of patients with PDAC have metastatic disease at the time of diagnosis, with a median overall survival (OS) of 6 months (2). In 1997, gemcitabine started to become the standard chemotherapy regimen for advanced PDAC (3). Since 2010, 2 new combination therapies have been more widely adopted as the standard of care systemic therapy for advanced PDAC, namely nab-paclitaxel/gemcitabine and FOLFIRINOX (4). In China, from the perspective of the healthcare system, nab-paclitaxel/gemcitabine may be a more cost-effective treatment option for metastatic PDAC compared with FOLFIRINOX (5).

Anlotinib is a novel small molecule multi-target tyrosine kinase inhibitor which can effectively inhibit VEGFR, PDGFR, FGFR, C-KIT, and other kinases (6), and has anti-tumor angiogenesis and tumor growth inhibition effects (7,8). Anlotinib is an anti-tumor class 1.1 new drug independently developed by China Chia Tai Tianqing Pharmaceutical Group. It was launched in May 2018 and was approved by China's National Medical Products Administration (NMPA) for the treatment of advanced non-small cell lung cancer (NSCLC) (8,9), small cell lung cancer (SCLC) (10), soft tissue sarcoma (11), thyroid cancer (12), and esophageal cancer (13). Clinical trials are currently underway in gastric, liver, kidney, colorectal, bile duct, breast, endometrial, cervical, ovarian, and head and neck cancers, along with metastatic pheochromocytoma or paraganglioma, glioma, diffuse large B cell lymphoma, NK/T cell lymphoma, Ewing's sarcoma, and many other cancers.

PDAC tissues have high expression of VEGF, which is associated with liver metastasis in PDAC and is predictive of poor prognosis (14). Anlotinib exerted noteworthy cytotoxicity on PDAC cells (15). Anlotinib can inhibit proliferation, induce G2/M phase arrest, and trigger apoptosis in PDAC and hepatocellular carcinoma (HCC) cell lines. It induces apoptosis of PDAC cells through the accumulation of reactive oxygen species (ROS) which activates endoplasmic reticulum (ER) stress via the PERK/p-eIF2α/ATF4 pathway (16,17). There are abundant vascular tissues in liver and kidney tumors, and the effective treatment results of anlotinib in these tumors suggests that it may have the same effect in PDAC (18,19).

At present, systemic chemotherapy remains the primary treatment for patients with metastatic PDAC to prolong survival time and improve life quality (20), but the overall efficacy is still unsatisfactory, only increasing the median survival by 2–4 months, and related to considerable toxicity (21). The timely addition of anlotinib to the nab-paclitaxel/gemcitabine regimen may further increase the treatment efficacy for PDAC, which has not yet been reported. Therefore, in this study, we aimed to evaluate the efficacy and safety of anlotinib combined with nab-paclitaxel/gemcitabine in the first-line treatment of patients with unresectable or metastatic PDAC and provide evidence for the treatment regimens of advanced PDAC, along with new indications of anlotinib. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-544/rc).

Methods

Study design

This was a retrospective cohort of patients diagnosed with unresectable or metastatic PDAC performed in The First Affiliated Hospital of Anhui Medical University from August 17, 2019 to April 3, 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (No. P2021-13-21). Signed informed consent was obtained from each patient.

Patients

Eligible patients were aged 18 years or older with unresectable or metastatic PDAC who had no systematic treatment for unresectable or metastatic PDAC, or who had received adjuvant or neoadjuvant chemotherapy with 1 regimen and relapsed 6 months after the end of chemotherapy. Other inclusion criteria were at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and expected survival time ≥12 weeks, and liver function of Child-Pugh grade A [5–6] or good grade B [7] and adequate organ function.

Patients who received anlotinib plus nab-paclitaxel/

gemcitabine treatment were defined as the anlotinib plus chemotherapy group and patients who received nab-paclitaxel/gemcitabine were defined as the chemotherapy group. The treatment method was chosen according to the patient's will.

Treatment

Nab-paclitaxel (260 mg/m^2) followed by gemcitabine (1,000 mg/m^2) were administered intravenously on day 1 every 3 weeks and gemcitabine (1,000 mg/m^2) was administered intravenously on day 8 every 3 weeks in the chemotherapy group. Anlotinib (12 mg) was taken orally before breakfast on days 1–14 every 3 weeks in the anlotinib plus chemotherapy group. If there was an omission but the interval between the next medication was less than 12 hours, no refill would be given. Subsequent nab-paclitaxel followed by gemcitabine was administered. Antiemetic treatment was administered prior to nab-paclitaxel/gemcitabine chemotherapy. Certain patients were given sodium bicarbonate to alkalinize the urine.

All patients received at least 2 cycles of chemotherapy and were allowed to receive local radiotherapy (except to the target lesion). The clinical data and follow-up information were obtained from the hospital records or by telephone.

Dose adjustment

During oral administration of anlotinib, adverse reactions were closely monitored and adjustments were made to ensure that it was well tolerated by patients. The adverse reactions could be treated by symptomatic treatment, suspension of medication, and/or adjustment of dosage. The first adjustment dosage was 10 mg once a day for 2 weeks in a 3-week cycle and the second adjustment dosage was 8 mg once a day for 2 weeks in a 3-week cycle. If 8 mg was not tolerated, the drug would be permanently discontinued. If grade 3 or higher hematological toxicities occurred, the dose of nab-paclitaxel and gemcitabine would be reduced by 25%. If there were grade 3 or higher non-hematological toxicities, nab-paclitaxel and/or gemcitabine would be discontinued until grade 0–1 or baseline levels were restored. Restarting nab-paclitaxel and/or gemcitabine therapy with a 25% lower dose was considered according to the investigator's judgment.

Outcomes

The size of the tumors was measured by computed tomography (CT), positron emission tomography (PET)/CT, and/or magnetic resonance imaging (MRI) at baseline, after every 2 cycles, and every 9 weeks during follow-up. Tumors were assessed using CT or MRI. The response to treatment was evaluated according to RECIST version 1.1. The primary outcomes were progression-free survival (PFS) and OS. Secondary outcomes were the objective response rate (ORR), the disease control rate (DCR), and toxic side effects. OS was defined as the time from treatment initiation until the date of death or last follow-up. PFS was defined as the time from treatment initiation to disease progression or to termination of the follow-up if no relapse or death from any cause occurred.

Clinical assessment

Tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were recorded. Hematological and other toxicities were evaluated every treatment cycle according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). During treatment, blood pressure, electrocardiogram, liver and kidney function, blood routine, urine routine, stool routine, blood coagulation function, and other indexes were closely observed. If any grade 3 or higher toxicity was observed, the dose of chemotherapy was decreased in the subsequent cycle.

Follow-up

Clinical data and follow-up information were mainly obtained from hospital records or by telephone. Medical follow-up letters were also used. The follow-up ended on July 30, 2021.

Statistical analysis

Statistical analysis was performed using SPSS, version 18.0. The tumor response, PFS rates, OS rates, and toxic side effects in the two groups were compared using the Fisher's exact probability test. The median OS (mOS) and median PFS (mPFS) were estimated with the Kaplan-Meier method, and were compared between the two groups using the log-rank test. Two-tailed probability value of $P<0.05$ was considered as statistically significant.

Results

Clinical characteristics

At the end of follow-up, a total of 33 patients were included in this study, with 17 cases in the anlotinib plus

chemotherapy group and 16 cases in the chemotherapy group (*Table 1*). There were 13 males and 20 females, with a median age of 66 years (48–84 years), and all patients were stage IV. There were 22 (66.7%) patients with multiple hepatic metastases and 11 (33.3%) patients with tumor metastasis after previous radical resection.

Efficacy evaluation

A total of 31 patients completed 2 cycles of treatment and 18 patients completed 4 cycles. Of these 18, there were 10 cases in the anlotinib plus chemotherapy group and 8 cases in the chemotherapy group. The tumor responses to treatment are shown in *Table 2*. There were 5 cases of partial response (PR) and 6 cases of stable disease (SD) in the anlotinib plus chemotherapy group, and 4 cases of PR and 4 cases of SD in the chemotherapy group, with no significant differences observed between the two groups. The mPFS of the anlotinib plus chemotherapy group was 5 months (95% CI: 4.97–5.94) while the mPFS of the chemotherapy group was 2.7 months (95% CI: 2.4–3.3; P=0.0220; *Figure 1*). The mOS of the anlotinib plus chemotherapy group was 9 months (95% CI: 6.55–11.45) while the mOS of the chemotherapy group was 6 months (95% CI: 1.08–10.92; P=0.0060; *Figure 2*). The 3- and 6-month PFS, and the 6- and 12-month OS of the anlotinib plus chemotherapy group were significantly higher than those of the chemotherapy group (P<0.05; *Tables 3*,*4*). Three patients in the anlotinib plus chemotherapy group received chemotherapy previously and had PR or SD again, therefore the disease control time increased by 3–5 months. CEA and CA19-9 decreased when treatment was effective.

Toxic side effects

Up to the last follow-up, hematological toxicities, leukopenia, and thrombocytopenia were observed in all patients (*Table 5*). Six patients in the anlotinib plus chemotherapy group and 5 patients in the chemotherapy group with grade 3 or higher hematological toxicities had their chemotherapy dose reduced. An 84-year-old woman was treated with oral anlotinib after 2 cycles of chemotherapy, and no serious hematological toxicity was observed. The proportion of patients with hematological toxicities in the anlotinib plus chemotherapy group was not significantly higher than that in the chemotherapy group. Hematological toxicity was not observed in patients who could not tolerate chemotherapy when anlotinib was retained orally. Blood pressure increased in 4 patients after oral administration of anlotinib, and blood pressure was maintained in the normal range after dose reduction and the addition of antihypertensive drugs. Five patients developed hand-foot syndrome in the anlotinib plus chemotherapy group. One patient developed diarrhea, which disappeared after nab-paclitaxel/gemcitabine was discontinued.

Discussion

In this study, we found that anlotinib plus nab-paclitaxel/gemcitabine for first-line treatment of PDAC was effective, with an ORR of 29.4%, a DCR of 64.7%, an mPFS of 5 months, and a mOS of 9 months. The PFS at 3 and 6 months, and the OS at 6 and 12 months in the anlotinib plus chemotherapy group were significantly higher than those in the chemotherapy group. Compared with nab-paclitaxel/gemcitabine chemotherapy, the regimen combined with anlotinib tended to have a longer OS and better tolerability.

EGFR overexpression was found in approximately 30% to 89% of PDAC cases (22). In a phase III randomized controlled clinical study (23), gemcitabine plus erlotinib showed positive results for advanced PDAC, but the mOS was only extended by 0.33 months (median 6.24 *vs.* 5.91 months). However, gemcitabine plus erlotinib were rarely used in clinical practice (24,25). Another prospective, multicenter phase II study (26) showed that the addition of cetuximab to gemcitabine standard adjuvant chemotherapy improved the prognosis of pancreatic cancer, with a median disease-free survival (DFS) of 10 months, a DFS rate of 27.1% at 18 months, and a mOS of 22.4 months. KRAS mutations are the most common genetic abnormality in PDAC patients and were detected in 95% of tumors (27,28). Nimotuzumab, an anti-EFGR monoclonal antibody, combined with gemcitabine was used as an active first-line regimen in KRAS wildtype patients with locally advanced or metastatic PDAC. It resulted in an mOS of 8.6 months and mPFS of 5.1 months for gemcitabine plus nimotuzumab, and an mOS of 6.0 months and mPFS of 3.4 months in the gemcitabine plus placebo group (P=0.0163) (29). Sotorasib (AMG510) is just beginning to hit the market in NSCLC (30), and there may be more studies in other tumors such as PDAC in the future.

PARP inhibitors in PDAC have focused on patients with germline or somatic BRCA1/2 or PALB2 mutations, which account for 14% of patients (31). The POLO study is the first randomized phase III study in PDAC screened

Table 1 Patient demographics and clinical characteristics

Sex	Age	Diagnosis at first visit	Metastatic site of pancreatic cancer	Stage	Treatment	First medication time	Cycle	Efficacy evaluation	PFS (months)	Treatment plan after progression	OS (months)	Outcome
F	66	2020/2/5	Multiple hepatic	IV	Anlotinib plus chemotherapy	2020/4/15	5	PR	5.0	Intraperitoneal chemotherapy	9	Death
M	66	2020/1/10	Retroperitoneal, splenic vein	IV	Anlotinib plus chemotherapy	2020/1/19	9	PR	7.5	Oxaliplatin + anlotinib	9	Death
M	64	2020/1/1	Retroperitoneal, splenic vein	IV	Anlotinib plus chemotherapy	2020/4/21	5	SD	4.0	Irinotecan + 5-Fu	9	Death
F	84	2020/4/27	Retroperitoneal	IV	Anlotinib plus chemotherapy	2020/4/28	5	PR	9.3	Anlotinib + capecitabine	12	Death
M	68	2020/7/9	Multiple hepatic metastases	IV	Anlotinib plus chemotherapy	2020/7/15	3	PD	1.8	Irinotecan + 5-Fu	5	Loss to follow-up
F	72	2020/8/2	Multiple hepatic metastases	IV	Anlotinib plus chemotherapy	2020/8/2	5	SD	5.1	Uncertain	8	Loss to follow-up
F	56	2020/9/5	Retroperitoneal	IV	Anlotinib plus chemotherapy	2020/9/7	4	SD	4.3	Particle + irinotecan + raltitrexed, anlotinib 5 months	10	Survival
F	65	2020/8/5	Multiple hepatics, lungs, adrenals	IV	Anlotinib plus chemotherapy	2020/9/25	3	PD	3.4	Uncertain	6	Death
F	64	2020/9/27	Multiple hepatics, lungs	IV	Anlotinib plus chemotherapy	2020/10/1	3	PD	5.3	Anlotinib	8	Loss to follow-up
F	67	2020/9/28	Multiple hepatic metastases	IV	Anlotinib plus chemotherapy	2020/10/22	4	SD	4.5	Anlotinib + sintilimab	9	Survival
M	52	2021/2/25	Multiple hepatics, spleen	IV	Anlotinib plus chemotherapy	2021/5/27	3	SD	2.0	Anlotinib + chemotherapy	2	Survival
M	80	2020/11/14	Multiple hepatic metastases	IV	Anlotinib plus chemotherapy	2020/11/14	3	PD	5.0	Anlotinib	8	Loss to follow-up
F	61	2020/11/4	Multiple hepatic metastases	IV	Anlotinib plus chemotherapy	2020/12/24	4	PD	3.0	Irinotecan + oxaliplatin	5	Loss to follow-up
M	53	2020/12/28	Multiple hepatics, lungs	IV	Anlotinib plus chemotherapy	2021/1/1	6	PR	6.9	Anlotinib + chemotherapy	7	Survival
F	57	2021/2/6	Multiple retroperitoneal, after surgery	IV	Anlotinib plus chemotherapy	2021/2/1	6	PR	5.9	Anlotinib + chemotherapy	6	Survival
F	58	2020/6/17	Multiple lungs, after surgery	IV	Anlotinib plus chemotherapy	2021/2/1	3	PD	2.4	Chemotherapy	6	Survival
F	58	2021/2/22	Multiple hepatic metastases	IV	Anlotinib plus chemotherapy	2021/3/1	2	SD	2.5	Uncertain	5	Survival
M	69	2019/8/17	Retroperitoneal	IV	Chemotherapy	2019/8/17	3	PD	2.7	S1	6.5	Death
F	71	2019/10/19	Multiple retroperitoneal, after surgery	IV	Chemotherapy	2019/12/14	4	SD	4.8	Oxaliplatin + S1	6	Death
F	68	2019/12/27	Multiple hepatic metastases	IV	Chemotherapy	2019/12/27	2	PD	1.7	Uncertain	4	Death
M	67	2020/3/6	Multiple hepatic metastases	IV	Chemotherapy	2020/3/6	1	PD	1.3	Supportive treatment	2	Death
M	57	2019/3/5	Multiple retroperitoneal, after surgery	IV	Chemotherapy	2020/3/19	5	PR	4.5	S1	4	Loss to follow-up
F	60	2020/3/13	Retroperitoneal	IV	Chemotherapy	2020/3/21	1	PD	1.3	Chinese medicine	3	Death
F	58	2020/7/23	Retroperitoneal	IV	Chemotherapy	2020/7/23	4	SD	4.0	Supportive treatment	4	Death
F	61	2020/6/	Multiple hepatic metastases after surgery	IV	Chemotherapy	2020/8/15	6	SD	5.1	PD after adjuvant chemotherapy ended after 3 months	11	Death
M	60	2020/7/13	Multiple retroperitoneal, after surgery	IV	Chemotherapy	2020/9/28	2	PD	1.5	Supportive treatment	3	Death

Table 1 (*continued*)

Table 1 (*continued*)

Sex	Age	Diagnosis at first visit	Metastatic site of pancreatic cancer	Stage	Treatment	First medication time	Cycle	Efficacy evaluation	PFS (months)	Treatment plan after progression	OS (months)	Outcome
M	64	2020/3/3	Multiple retroperitoneal, after surgery	IV	Chemotherapy	2020/10/18	4	SD	2.7	Supportive treatment	3	Death
F	69	2020/9/10	Multiple hepatics, after surgery	IV	Chemotherapy	2020/10/24	5	PR	5.8	Chemotherapy	9	Survival
F	53	2020/12/1	Multiple hepatic	IV	Chemotherapy	2020/12/3	2	PD	1.9	S1	4	Death
M	48	2020/12/18	Multiple hepatic	IV	Chemotherapy	2020/12/24	6	PR	5.8	Anlotinib	7	Survival
F	59	2021/2	Multiple hepatic	IV	Chemotherapy	2021/3/3	5	PR	2.9	Supportive treatment	5	Survival
M	57	2021/2/4	Multiple hepatics, after surgery	IV	Chemotherapy	2021/3/23	3	PD	2.0	Supportive treatment	4	Survival
F	58	2021/2/18	Multiple hepatics, after surgery	IV	Chemotherapy	2021/4/3	3	PD	2.1	Irinotecan + 5-Fu	4	Survival

PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival; OS, overall survival.

by biomarkers (NCT02184195). Patients who achieved disease stabilization after at least 4 months of platinum-based therapy were randomized to olaparib or placebo maintenance therapy, with an mPFS of 7.4 and 3.8 months, respectively (P<0.004), and a median remission duration of 24.9 months. This result suggested that some germline BRCA patients benefited from olaparib maintenance therapy. However, there were no differences in the mOS between the olaparib and placebo groups (median, 18.9 *vs.* 18.1 months; P=0.68). The incidence of grade 3 or higher adverse events was 40% in the olaparib group and 23% in the placebo group.

Two studies targeting CDK4/6 inhibitors in combination with mTOR inhibitors or paclitaxel are ongoing in PDAC (32,33). Other studies targeting low-incidence, operable mutations are ongoing, some with relatively significant results (34,35). However, this requires routine gene sequencing of tumor tissue from advanced patients within a clinically operable time frame to identify and treat subpopulations of patients with these rare changes. Therefore, for most PDAC patients, cytotoxic chemotherapy and the search for broad-spectrum targeted therapies will be the focus of exploration.

Anlotinib is a novel oral RTK inhibitor targeting VEGFR-2 and -3, PDGFR-α and -β, FGFR1-4, C-KIT and Ret, thereby inhibiting tumor growth and angiogenesis. Anlotinib significantly suppressed VEGF/PDGF-BB/FGF-2-induced angiogenesis *in vitro* and *in vivo*. A previous study demonstrated anlotinib also inhibits the activation of VEGFR2, PDGFRβ, FGFR1 and downstream ERK signaling (36). Since anlotinib was launched as a broad-spectrum antitumor targeted drug, a large amount of important data has been obtained in the treatment of tumors. Anlotinib combined with immunotherapy has not been yet reported in the treatment of PDAC. At present, a study on PDAC have been carried out (NCT04764084). This study was designed to explore the clinical efficacy of anlotinib combined with Anti-PD-1 antibody AK105 in the treatment of third- and above-line advanced pancreatic cancer patients, in order to optimizing treatment strategy for PDAC patients. Additionally, anlotinib plus immunotherapy has been well elucidated in various solid tumors. In lung cancer, third-line monotherapy (37) or second-line chemotherapy (38,39) combined with immunotherapy (40) has been effectively applied. Studies have achieved effective results not only in NSCLC and SCLC (10), but also in liver cancer (19,41) or refractory metastatic colorectal cancer (42). There are currently more

Table 2 Tumor response to treatment

Tumor response	Anlotinib plus chemotherapy (n=17) (%)	Chemotherapy (n=16) (%)	P
CR	0	0	–
PR	5 (29.40)	4 (25.0)	>0.999
SD	6 (35.29)	4 (25.0)	0.708
PD	6 (35.29)	8 (50.0)	0.491
ORR	5 (29.40)	4 (25.0)	>0.999
DCR	11 (64.70)	8 (50.0)	0.491

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

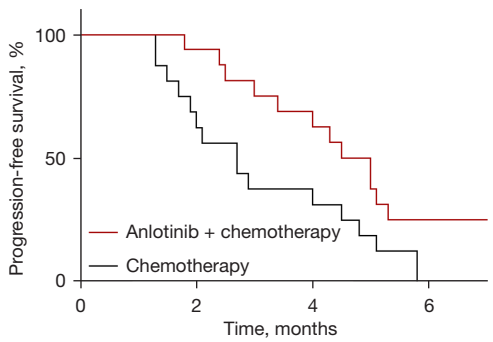

Figure 1 The median progression free survival (mPFS) of the anlotinib plus chemotherapy group was 5 months (95% CI: 4.97–5.94) while the mPFS of the chemotherapy group was 2.7 months (95% CI: 2.4–3.3; P=0.0220). CI, confidence interval.

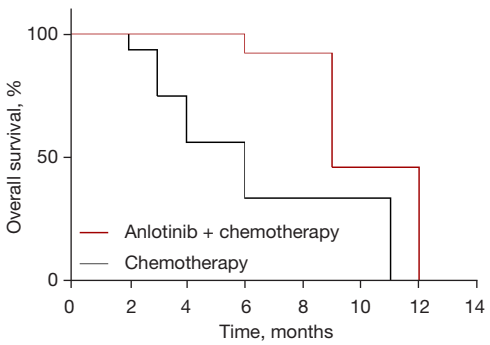

Figure 2 The median overall survival (mOS) of the anlotinib plus chemotherapy group was 9 months (95% CI: 6.55–11.45) while the mOS of the chemotherapy group was 6 months (95% CI: 1.08–10.92; P=0.0060). CI, confidence interval.

Table 3 PFS rates in the two groups

PFS	Anlotinib plus chemotherapy (n=17) (%)	Chemotherapy (n=16) (%)	P
3 months	13 (76.47)	6 (37.50)	<0.001
6 months	3 (17.65)	0	<0.001
12 months	0	0	–

PFS, progression-free survival.

Table 4 OS rates in the two groups

OS	Anlotinib plus chemotherapy (n=17) (%)	Chemotherapy (n=16) (%)	P
3 months	16 (94.12)	15 (93.75)	0.655
6 months	13 (76.47)	5 (31.25)	0.000
12 months	1 (5.88)	0	0.004

OS, overall survival.

Table 5 Toxic side effects in the two groups

Toxic side effects	Anlotinib plus chemotherapy (n=17) (%)	Chemotherapy (n=16) (%)	P
Hematological toxicity			>0.999
< Grade 3	11 (64.71)	11 (68.75)	
≥ Grade 3	6 (35.29)	5 (31.25)	
Non-hematological toxicity*			
Hypertension	4 (23.53)	0	0.103
Hand-foot syndrome	5 (29.41)	0	0.045
Diarrhea	1 (5.88)	0	>0.999

*, no grade 3 or higher non-hematological toxicity was observed in all patients.

than 230 registered clinical studies underway in multiple types of tumors. Anlotinib may induce apoptosis and inhibit the proliferation of HCC (17) and colon cancer cells (43) by inhibiting the expression of Bcl-2 and survivin or by inactivating the ERK and Akt pathways and the PI3K/Akt pathway.

Yang *et al.* (16) found that anlotinib could induce ROS through the PERK/peIF2α/ATF4 pathway to activate ER stress, inhibit cell proliferation, induce G2/M phase arrest, and induce apoptosis, which led to PDAC cell apoptosis. Zhang *et al.* (15) revealed that anlotinib had a profound inhibitory effect on ribosomes, and regulated the cell cycle, RNA metabolism, and lysosomes as determined by transcriptomics, proteomics, and phosphor proteomics profiling. These studies suggested that anlotinib plus chemotherapy was a feasible regimen for the treatment of PDAC. In our study, we found that anlotinib plus nab-paclitaxel/gemcitabine could prolong PFS and OS in the first-line treatment of unresectable advanced PDAC patients. Interestingly, there were 3 patients who did not receive anlotinib therapy before nab-paclitaxel/gemcitabine chemotherapy. However, further shrinkage of the cervical lymph nodes, improvement of quality of life, and decreased tumor markers were observed after the addition of anlotinib to the original chemotherapy regimen. This suggested that anlotinib was effective in the treatment of PDAC.

At present, the combination of immunotherapy + multi-target drugs, including pembrolizumab + lenvatinib, camrelizumab + apatinib, sintilimab + anlotinib, have all obtained positive results in liver cancer. These treatment regimens maybe potential therapeutic strategy for patients with advanced PDAC. In addition, PD-L1 combined with multi-targeted drugs or combined with chemotherapy drugs, PD-1/CTLA4 antibody, antibody-conjugated drugs may be studied in PDAC in the future. A case report for the successful application of anlotinib in pancreatic cancer have been reported (44).

A previous study on the monotherapy and combination therapy of anlotinib found that the side effects of anlotinib were relatively mild, and the proportion of cases with dose downregulation or drug discontinuation due to side effects was not high (45). The most common adverse events (≥20%) of anlotinib are hypertension, fatigue, hand-foot skin reactions, gastrointestinal reactions, abnormal liver function, abnormal thyroid function, hyperlipidemia and proteinuria. But the incidence of adverse events and serious adverse events is lower than apatinib, regorafenib, and sorafenib. When patients received anlotinib, blood pressure should be measured and bleeding, thrombotic events and hand-foot syndrome should be observed. The presence of hand-foot syndrome is reported to be associated with prolonged survival, which may be a potential clinical marker for the treatment of NSCLC with anlotinib (46). Furthermore, liver and thyroid function, and urine routine should be payed attention during long-term anlotinib treatment. The most likely problem with our treatment method in this study is how to reduce the side effects of chemotherapy, which is also a common reaction of chemotherapy drugs. It was necessary to reduce the dose of chemotherapy drugs in the treatment of advanced PDAC for elderly patients and patients with high ECOG scores. In addition, if there is abnormal blood coagulation and blood pressure is difficult to control, this regimen should be carefully used. Clinical trials of anlotinib in combination with immunotherapy have been conducted in liver, esophageal, and lung cancer with positive results. Anlotinib combination therapy in pancreatic cancer is underway, and the final results are eagerly anticipated.

The small sample size was one of the limitations of this study and our results from the direct comparisons are at high risk of bias. Therefore, randomized controlled trials with large sample sizes are warranted to further evaluate the treatment effects of anlotinib in PDAC.

In conclusion, compared with nab-paclitaxel/gemcitabine chemotherapy, anlotinib plus nab-paclitaxel/gemcitabine as a first-line treatment regimen is safe and may prolong survival in patients with unresectable or metastatic PDAC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-544/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-544/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study obtained approval from the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (No. P2021-13-21). Signed informed consent was obtained from each patient.

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