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ORIGINAL ARTICLE

Synergistic effect of additional anlotinib and immunotherapy as second-line or later-line treatment in pancreatic cancer: A retrospective cohort study

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None

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is in urgent need of a second-line or later-line treatment strategy. We aimed to analyze the efficacy and safety of additional anlotinib, specifically anlotinib in combination with immunotherapy, in patients with PDAC who have failed first-line therapy.

Methods: Patients with pathological diagnosis of PDAC were additionally treated with anlotinib, and some patients were treated with anti-PD-1 agents at the same time, which could be retrospectively analyzed. The efficacy and safety of additional anlotinib were evaluated.

Results: A total of 23 patients were included. In patients treated with additional anlotinib, the overall median progression-free survival (PFS) was 1.8 months and the median overall survival (OS) was 6.3 months, regardless of anti-PD-1 agents. Among patients receiving additional anlotinib in combination with anti-PD-1 agents, median PFS and OS were 1.8 and 6.5 months, respectively. Adverse events (AEs) were observed in 16 patients (69.6%). In patients treated with additional anlotinib, the majority of AEs were grade 1–3. Univariate analysis revealed that patients with baseline red blood cell distribution width (RDW) <14% treated with additional anlotinib plus anti-PD-1 agents had significantly longer OS than patients with baseline RDW ≥14% ($p = 0.025$). Patients with additional anlotinib plus anti-PD-1 agents as second-line therapy had a longer OS than those treated as later-line therapy ($p = 0.012$). Multivariate analysis showed that baseline RDW was the only independent risk factor for OS ($p = 0.042$).

Abbreviations: AE, adverse event; CR, complete response; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; RDW, red blood cell distribution width; SD, stable disease.

Boyu Qin, Qi Xiong, and Lingli Xin contributed equally to this study and shared the first authorship.

Conclusion: The combination of anlotinib and immunotherapy represents an effective add-on therapy with tolerable AEs as second- or later-line therapy in patients with PDAC, particularly in patients with baseline RDW <14%.

KEYWORDS
anlotinib, efficacy, immunotherapy, independent risk factors, pancreatic ductal adenocarcinoma

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death worldwide, with an increasing incidence, and is considered the most lethal malignancy, with a 5-year survival rate of less than 10% [1]. Even for patients with resectable PDAC, the 5-year survival rate is only about 20% [2]. Unfortunately, 85% of patients with PDAC are diagnosed with advanced or metastatic disease. For these patients, FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) or gemcitabine plus nab-paclitaxel is recommended as first-line therapy [3]. Most patients have disease progression approximately 6 months after first-line therapy. However, there is currently no preferred second-line treatment option. Therefore, there is an urgent need for new and effective treatment strategies for subsequent treatment.

Angiogenesis and vascular abnormalities are regulated by vascular endothelial growth factor (VEGF) and other proangiogenic factors and are critical for tumor growth and metastasis. Drugs that target angiogenesis have shown promising effects in prolonging the survival of cancer patients, including lung, ovarian, and other cancers. Unfortunately, antiangiogenesis therapy alone or in combination with chemotherapy has failed to improve OS in patients with pancreatic cancer [4–6]. Anlotinib is a tyrosine kinase inhibitor (TKI) that targets a variety of tumor angiogenesis and proliferation signaling receptors and has strong antitumor activity in various cancer types such as lung cancer, soft tissue sarcoma, and thyroid carcinoma. Even in small-cell lung cancer (SCLC), a highly aggressive cancer, anlotinib significantly prolongs PFS and OS [7]. Several case reports have reported the role of anlotinib in advanced pancreatic cancer [8, 9], suggesting that anlotinib may exert a potent antitumor effect in PDAC.

Anti-programmed cell death protein-1 (PD-1) and programmed cell death protein ligand-1 (PD-L1) agents have remarkably changed the treatment strategies for many cancers, such as melanoma, lung cancer, renal cell carcinoma, head and neck cancer, and so on. However, anti-PD-1/PD-L1 agents alone benefit only about 20% of patients with nonselective cancers, while patients with PDAC benefit negligible from anti-PD-1/PD-L1 agents. Therefore, the strategy of combining anti-PD-1/PD-L1 agents with other therapies has attracted widespread attention. Studies have shown that anti-PD-1/PD-L1 agents in combination with anti-angiogenetic therapy may improve treatment outcomes by remodeling abnormal vasculature and promoting immune effector cell infiltration into tumors [10]. Antiangiogenic combined anti-PD-1 agents have shown promising antitumor activity in patients with hepatocellular carcinoma, renal cell carcinoma, gastric cancer, and endometrial cancer in multiple early-stage clinical trials [11–14]. Meta-analysis results of antiangiogenic combined anti-PD-1 agents also confirmed the clinical benefit in patients with renal cell carcinoma, with improved survival and a more than threefold increase in complete response (CR) rates [15, 16]. Meanwhile, combination therapy with anti-angiogenic and anti-PD-1 agents has been evaluated as front-line treatment for patients with advanced hepatocellular carcinoma (HCC) [17].

As a novel antiangiogenic agent, anlotinib in combination with anti-PD-1 agents as first-line or later-line therapy has significantly improved the objective response rate (ORR), disease control rate (DCR), and PFS in patients with non-small cell lung cancer [18–20]. We hypothesize that additional anlotinib plus anti-PD-1 agents may provide a survival benefit in patients with PADC. In this study, we retrospectively analyzed the therapeutic advantages of additional anlotinib in combination with anti-PD-1 agents as a second-line or later-line treatment in PDAC.

2 | METHODS

2.1 | Patients and treatment schedules

The efficacy and safety of the addition of anlotinib alone and anlotinib plus anti-PD-1 agents as second- or later-line treatment in PDAC were retrospectively analyzed. Between February 2019 and February 2021, this retrospective study included patients with a pathologic diagnosis of PDAC at the General Hospital of the

Chinese PLA who received additional anlotinib with or without anti-PD-1/PD-L1 agents as second- or later-line therapy. All patients progressed after first-line therapy. This study was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army (No. S2021-553-01) and was carried out in accordance with the principles of the Declaration of Helsinki. Given the retrospective nature of this study, informed consent was waived. Clinical parameters of patients were collected, including sex, age, stage, presence or absence of liver/brain metastases, performance status of Eastern Cooperative Oncology Group (ECOG PS), history of smoking/alcohol consumption, previous treatment lines and regimens, radiotherapy history, and radiologic and laboratory data.

Anlotinib was administered once daily (12 mg or 8 mg) for 14 days and discontinued for 7 days within a cycle. The initial dose was determined by the oncologist based on the patient's condition. The dose of combination therapy was determined according to the guidelines of the National Comprehensive Cancer Network of the Chinese Society of Clinical Oncology. All patients were followed up inpatient or outpatient. The follow-up period was monthly, at least once in each follow-up period. Follow-up data were collected up to January 2022.

2.2 | Evaluation

Two physicians independently interpreted computed tomography (CT) or magnetic resonance imaging (MRI) scans according to Response Evaluation Criteria in Solid Tumors (RESICT) version 1.1 to assess treatment efficacy. Assessments were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). If there was a disagreement on the efficacy evaluation, a third physician should be hired for a supplementary evaluation, and a consensus should be reached after a thorough discussion. The duration from the time of anlotinib administration to the occurrence of PD or death of any cause before PD was defined as PFS. The time from initiation of anlotinib administration to death was defined as OS. The rates of CR and PR were used to calculate ORR, and the rates of CR, PR, and SD were used to calculate DCR. Adverse events (AEs) were classified using the Common Terminology Criteria for Adverse Events version 5.0.

2.3 | Statistical analysis

Continuous variables were described as median and 95% confidence intervals (CI) or ranges. Categorical variables were reported as frequency or percentage. According to previous studies, the cutoff value for RDW was set at 14% [21, 22]. The chi-square test and Fisher's exact test were used to compare the differences between the two groups. Analysis of variance (ANOVA) was used to compare the differences between the three groups. Survival curves for PFS and OS were analyzed using the Kaplan–Meier method. The log-rank test was used for univariate analysis between groups. Cox regression analysis was used to analyze statistically significant risk factors according to the results of univariate analysis. The risk factor of $p < 0.1$ in univariate analysis was considered significant and was imported into Cox regression analysis. Statistical analysis was performed using PRISM version 8.0 (GraphPad Software) and SPSS version 25.0 (IBM Corp.). Statistical significance was defined as two-tail $p < 0.05$.

3 | RESULTS

3.1 | Clinical characteristics of patients treated with additional anlotinib

A total of 23 patients were included in the analysis. The median age was 58 years (range: 31–69 years). Seventeen patients (73.9%) reported no history of alcohol consumption, and 16 patients (69.6%) had no history of smoking. Twenty-two patients (95.7%) were diagnosed with stage IV, while one patient was diagnosed with stage III. Liver metastasis occurred in 17 patients (73.9%). Eleven patients had a baseline red blood cell distribution width (RDW) of less than 14%, and the other 12 patients had a baseline RDW of more than 14%. Nab-paclitaxel plus tegafur or nab-paclitaxel plus gemcitabine were chosen as first-line therapy. In some patients, chemotherapy agents or combinations of agents not used in first-line regimens (e.g., gemcitabine, capecitabine, XELOX, or FOLFRINOX) were selected as the basic treatment in second- or later-line therapy, and targeted agents (e.g., nimotuzumab or olaparib) might be added depending on the patient. Of all patients, 17 received physician-determined chemotherapy with the addition of anlotinib plus anti-PD-1 agents, including sintilimab, toripalimab, and pembrolizumab. The remaining six patients were treated with anlotinib in combination with chemotherapy or radiotherapy. Twelve patients (52.2%) received anlotinib as second-line therapy, and 11 patients received anlotinib as later-line therapy. Median follow-up was 6.3 months (range: 2.2–21.5 months). A detailed summary of the clinical features is provided in Table 1.

TABLE 1 Demographics and baseline characteristics of PDAC patients receiving additional anlotinib treatment.

Characteristics	Total ($n = 23$)	Anlotinib plus anti-PD-1 ($n = 17$)
Gender, *n* (%)		
Male	12 (52.2)	9 (52.9)
Female	11 (47.8)	8 (47.1)
Age, *n* (%)		
Median age, years (range)	58 (31–69)	58 (31–69)
≤60	15 (65.2)	10 (58.8)
>60	8 (34.8)	7 (41.2)
Clinical stage, *n* (%)		
III	1 (4.3)	0 (0.0)
IV	22 (95.7)	17 (100.0)
Liver metastases, *n* (%)		
No	6 (26.1)	5 (29.4)
Yes	17 (73.9)	12 (70.6)
Brain metastases, *n* (%)		
No	22 (95.7)	16 (94.1)
Yes	1 (4.3)	1 (5.9)
Lung metastases, *n* (%)		
No	20 (87.0)	14 (82.4)
Yes	3 (13.0)	3 (17.6)
Drinking history, *n* (%)		
Never drinking	17 (73.9)	11 (64.7)
Current drinker	4 (17.4)	4 (23.5)
Former drinker	2 (8.7)	2 (11.8)
Smoking history, *n* (%)		
Never smoked	16 (69.6)	12 (70.6)
Current smoker	3 (13.0)	3 (17.6)
Former smoker	4 (17.4)	2 (11.8)
ECOG PS, *n* (%)		
≤1	18 (78.3)	15 (88.2)
>1	5 (21.7)	2 (11.8)
No. of previous treatment lines, *n* (%)		
<3	12 (52.2)	9 (52.9)
≥3	11 (47.8)	8 (47.1)
Combined treatment, *n* (%)		
Chemotherapy/ Radiotherapy	6 (26.1)	0 (0.0)
Immunotherapy	17 (73.9)	17 (100.0)
Baseline RDW, *n* (%)		
<14%	11 (47.8)	7 (41.2)
≥14%	12 (52.2)	10 (58.8)

Abbreviation: RDW, red blood cell distribution width.

3.2 | Efficacy of additional treatment with anlotinib

Out of a total of 23 patients, 2 patients achieved PR, 7 achieved SD, and 14 developed PD. The overall ORR and DCR were 8.7% and 39.1%, respectively. Median PFS was 1.8 months and median OS was 6.3 months (Figure 1a,b).

Of the 17 patients who received anlotinib in combination with immunotherapy, two were evaluated for PR, three for SD, and 12 for PD. The ORR and DCR were 11.8% and 29.4% (Table 2). Median PFS and OS were 1.8 and 6.5 months, respectively (Figure 1a,b), both of which were similar to those of patients overall. Considering that only six patients received additional anlotinib alone, it was not possible to analyze the comparison between anlotinib in combination with immunotherapy and anlotinib alone. However, our results did suggest a slight prolongation of OS in patients treated with anlotinib in combination with anti-PD-1 agents.

We then sought to identify features that primarily contribute to the benefit of additional anlotinib in combination with immunotherapy in patients with PDAC. Results revealed that the OS was significantly longer in patients with baseline RDW <14% than in patients with baseline RDW ≥14% (median OS: 11.2 vs. 4.4 months; hazard ratio (HR): 0.66, 95% CI: 0.08–0.84; $p = 0.025$) (Figure 2a). We also found prolonged OS in patients who received additional anlotinib in combination with anti-PD-1 agents as second-line therapy compared with patients treated third or later (median OS: 9.9 vs. 3.2 months; HR: 0.21, 95% CI: 0.06–0.72; $p = 0.012$) (Figure 2b and Table 3). Subsequent Cox regression analysis confirmed that baseline RDW (HR [95% CI]: 4.70 (1.06–20.80), $p = 0.042$) was the only independent risk factor for OS in patients treated with additional anlotinib in combination with anti-PD-1 agents.

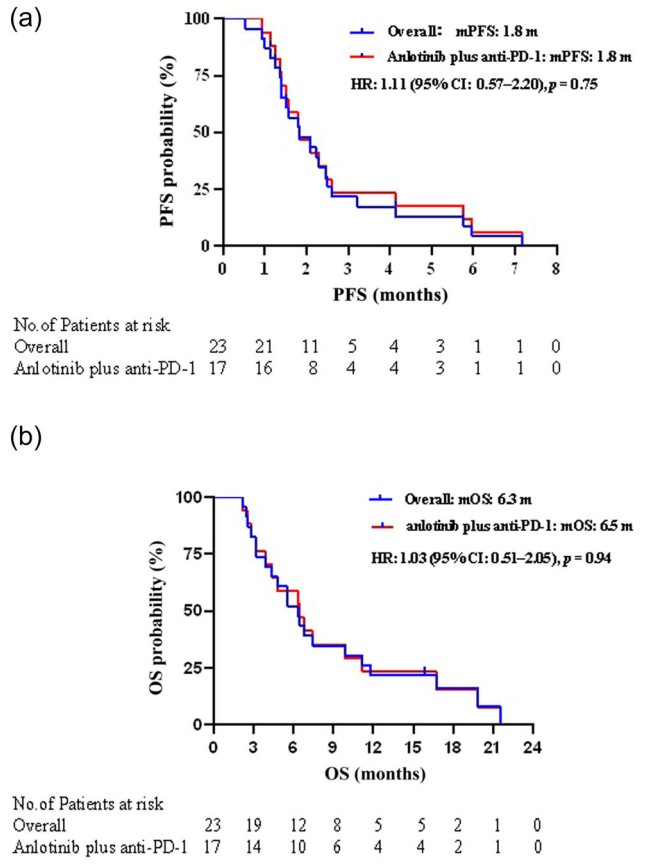

FIGURE 1 Median progression-free survival (a) and overall survival (b) between all included patients and those treated with anlotinib plus anti-PD-1. CI, confidence interval; HR, hazard ratio.

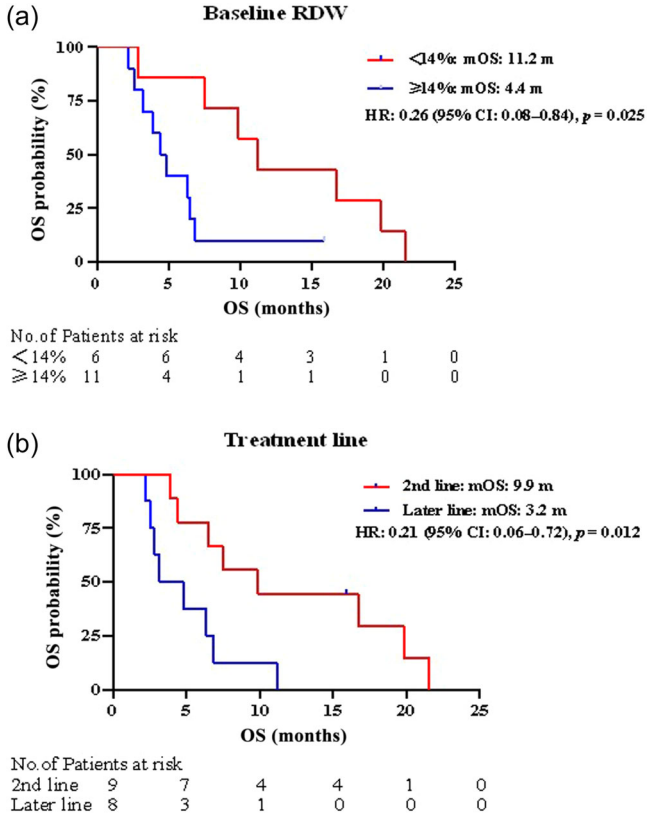

FIGURE 2 Median overall survival (OS) comparison between patients receiving additional anlotinib plus anti-PD-1 agents with a baseline RDW of <14% and patients with a baseline RDW of ≥14% (a). Median OS comparison between patients receiving additional anlotinib plus anti-PD-1 agents as second-line therapy and those receiving third- or later-line therapy (b).

TABLE 2 Overall response of additional anlotinib treatment.

	Overall ($n = 23$)	Anlotinib plus anti-PD-1 ($n = 17$)
CR	0	0
PR	2	2
SD	7	3
PD	14	12
ORR	8.7%	11.8%
DCR	39.1%	29.4%

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

3.3 | Safety of additional treatment with anlotinib

AEs were observed in 16 (69.6%) of 23 patients. In patients receiving additional anlotinib with or without anti-PD-1 agents, the majority of AEs were grade 1 to 3. Two patients reported elevated total bilirubin and/or direct bilirubin for grade 4 AEs, and one patient discontinued anlotinib due to AEs. Among the two patients, one was treated with anlotinib plus capecitabine and one was treated with anlotinib in combination with radiotherapy. The most common AEs reported were fatigue (21.7%), elevated aspartate transaminase (AST) (17.4%), elevated alanine transaminase (ALT) (17.4%), and hypokalemia (17.4%). The most common AEs in patients receiving additional anlotinib in combination with immunotherapy were fatigue (23.5%), hypokalemia (23.5%), and hand-foot syndrome (17.6%). No treatment-related deaths were observed. Immunotherapy treatment did not add an additional safety risk (Table 4).

4 | DISCUSSION

A subset of patients with PDAC who have progressed on standard first-line chemotherapy still have a good performance status sufficient for second- or later-line therapy. Currently, chemotherapy is generally recommended as a

TABLE 3 Univariable analysis of progression-free survival and overall survival in anlotinib plus immunotherapy.

		PFS		OS	
Characteristics	**Total ($n = 17$)**	**mPFS (95% CI)**	***p* value**	**mOS (95% CI)**	***p* value**
Gender, *n* (%)			0.851		0.444
Male	9 (52.9)	1.83 (1.070–2.590)		6.33 (1.860–10.800)	
Female	8 (47.1)	1.8 (0.553–3.047)		7.47 (0.000–15.786)	
Age, *n* (%)			0.949		0.451
≤60	10 (58.8)	1.8 (0.979–2.621)		6.33 (3.742–8.918)	
>60	7 (41.2)	1.83 (0.727–2.933)		7.47 (0–16.708)	
Clinical stage, *n* (%)			–		–
III	0 (0)	–		–	
IV	17 (100)	1.83 (1.117–2.543)		6.47 (3.741–9.199)	
Liver metastases, *n* (%)			0.151		0.436
No	5 (29.4)	2.47 (2.105–2.835)		9.87 (2.269–17.471)	
Yes	12 (70.6)	1.5 (1.211–1.789)		4.8 (1.286–8.314)	
Brain metastases, *n* (%)			0.000		0.053
No	16 (94.1)	1.83 (1.242–2.418)		6.47 (5.490–7.450)	
Yes	1 (5.9)	0.93		2.83	
Lung metastases, *n* (%)			0.261		0.437
No	14 (82.4)	1.57 (1.020–2.120)		4.8 (1.262–8.338)	
Yes	3 (17.6)	4.13 (1.201–7.059)		9.87 (6.029–13.711)	
Drinking history, *n* (%)			0.541		0.925
Never drinked	11 (64.7)	1.8 (1.336–2.264)		4.8 (1.606–7.994)	
Current drinker	4 (23.5)	1.57 (0–4.706)		6.47 (0.000–13.369)	
Former smoker	2 (11.8)	2.47		6.33	
Smoking history, *n* (%)			0.711		0.949
Never smoked	12 (70.6)	1.8 (1.240–2.360)		4.8 (0.675–8.925)	
Current smoker	3 (17.6)	1.57 (0.546–2.594)		6.47 (0.645–12.295)	
Former smoker	2 (11.8)	2.47		6.33	
ECOG PS, *n* (%)			0.198		0.000
≤1	15 (88.2)	2.1 (1.178–3.022)		6.83 (5.391–8.269)	
>1	2 (11.8)	1.37		2.2	
No. of previous treatment lines, *n* (%)			0.217		0.012
<3	9 (52.9)	2.3 (0.167–4.433)		9.87 (2.858–16.882)	
≥3	8 (47.1)	1.8 (1.162–2.438)		3.17 (0.440–5.900)	
Baseline RDW, *n* (%)			0.409		0.025
<14%	7 (41.2)	2.6 (1.830–3.370)		11.17 (7.834–14.506)	
≥14%	10 (58.8)	1.57 (1.105–2.035)		4.4 (2.959–5.841)	

Note: – represents none patients were in stage III.

Abbreviations: OS, overall survival; PFS, progression-free survival; RDW, red blood cell distribution width.

TABLE 4 Safety analysis of additional anlotinib treatment.

	Total ($n = 23$)		Anlotinib plus anti-PD-1 ($n = 17$)	
Adverse event	**Any grade**	**≥3 grade**	**Any grade**	**≥3 grade**
Fatigue, *n* (%)	5 (21.7)	1 (4.3)	4 (23.5)	1 (5.9)
Increased AST, *n* (%)	4 (17.4)	0 (0.0)	1 (5.9)	0 (0.0)
Increased ALT, *n* (%)	4 (17.4)	0 (0.0)	1 (5.9)	0 (0.0)
Hypokalemia, *n* (%)	4 (17.4)	1 (4.3)	4 (23.5)	1 (5.9)
Increased Tbil, *n* (%)	3 (13.0)	2 (8.7)	1 (5.9)	0 (0.0)
Increased Dbil, *n* (%)	3 (13.0)	2 (8.7)	1 (5.9)	0 (0.0)
Hand-foot syndrome, *n* (%)	3 (13.0)	0 (0.0)	3 (17.6)	0 (0.0)
Hypertension, *n* (%)	2 (8.7)	1 (4.3)	2 (11.8)	1 (5.9)
Rash, *n* (%)	2 (8.7)	0 (0.0)	2 (11.8)	0 (0.0)
Nausea, *n* (%)	2 (8.7)	0 (0.0)	2 (11.8)	0 (0.0)
Oral mucositis, *n* (%)	2 (8.7)	0 (0.0)	2 (11.8)	0 (0.0)
Increased Scr, *n* (%)	1 (4.3)	0 (0.0)	1 (5.9)	0 (0.0)
Neurotoxicity, *n* (%)	1 (4.3)	0 (0.0)	1 (5.9)	0 (0.0)
Leucopenia, *n* (%)	1 (4.3)	0 (0.0)	1 (5.9)	0 (0.0)
Thrombocytopenia, *n* (%)	1 (4.3)	0 (0.0)	1 (5.9)	0 (0.0)
Decreased hemoglobin count, *n* (%)	1 (4.3)	0 (0.0)	1 (5.9)	0 (0.0)
Diarrhea, *n* (%)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; Dbil, direct Bilirubin; Scr, serum creatinine; Tbil, total bilirubin.

second-line or later therapy for patients with PDAC, with median OS ranging from 2.3 to 6.1 months [23, 24]. In this study, we compared additional anlotinib and anlotinib in combination with immunotherapy as only six patients received additional anlotinib alone. We found that patients with PDAC who received anlotinib in combination with chemotherapy had an OS of 6.3 months, regardless of immunotherapy. We also found that the addition of anlotinib to second-line therapy was associated with longer OS compared with later-line anlotinib ($p = 0.012$). Our findings suggest that additional anlotinib may be a valid add-on option recommended for PDAC patients, which shows similar results as reported by Zhan et al. [25]. The advantage of anlotinib combination therapy may be due to the fact that PDAC has a special tumor microenvironment with dense interstitium, which is an important reason for the poor response of chemotherapy alone [26]. Although second- and later-line OS outcomes are influenced by tumor severity, there is a trend toward the addition of anlotinib to early-line therapy, particularly second-line therapy, to achieve greater benefit.

Combination therapy strategies such as molecularly targeted therapy, chemotherapy, and radiotherapy that can alter the tumor microenvironment to reveal potential effects in overcoming immunotherapy resistance. Previous studies by us and others have demonstrated that anlotinib enhances the efficacy of immunotherapy for lung cancer [27–29]. We found a slight prolongation of OS in patients with PDAC who received additional anlotinib plus immunotherapy. We speculate that the small sample size in this study may be partly attributable to this. In addition, this may also be due to the biological nature of PDAC, which is considered to be immunologically "cold" tumor, characterized by insufficient abundance of $CD8^+$ T cells [30]. Previous studies have reported that the underlying mechanism of resistance to PDAC immunotherapy lies in its unique genetic landscape, including mutations in *KRAS*, *TP53*, *CDKN2A*, and/or *SMAD4* in more than half of patients [31]. These findings may explain the unsatisfactory response to PDAC immunotherapy. However, many PDAC patients do benefit from immunotherapy, such as those with high microsatellite instability. Therefore, there is a need for biomarkers that distinguish responders from drug-resistant PDAC patients.

RDW is a parameter that reflects the degree of erythrocyte heterogeneity, which mirrors erythrocyte homeostasis, which may be attributed to oxidative stress, inflammation, nutritional status, and so on [32]. Several studies have shown that RDW is associated with the prognosis and diagnosis of many cancers, including

ovarian cancer, non-small cell lung cancer, and breast cancer [33]. Pedrazzani et al. showed that colorectal cancer patients with RDW above 14.1% had significantly worse OS in metastatic cancer treated with chemotherapy [21], and Patel et al. reported that the median OS of patients in the RDW >13.9% group was shorter than in the RDW <13.9% group, suggesting that RDW is an independent risk factor for survival outcomes in metastatic cancer receiving chemotherapy [34]. Since there is no variable cutoff for RDW in PDAC, we prefer 14% as the optimal value based on previous studies. Encouragingly, our results suggest that patients with PDAC with a baseline RDW of <14% are more likely to benefit from additional anlotinib in combination with anti-PD-1 agents with an OS of 11.2 months compared to 4.4 months with a baseline RDW of ≥14%. Therefore, in the present study, we add that RDW may be a predictive biomarker for PDAC patients receiving additional anlotinib in combination with immunotherapy.

As for safety issues, additional anlotinib with or without immunotherapy was tolerable. The most common AEs were fatigue, elevated AST or ALT, hand-foot syndrome, and hypokalemia. Two patients treated with additional anlotinib reported a grade 4 direct bilirubin elevation. We judged serious AEs to be due to bile duct obstruction caused by the tumor itself, rather than treatment. As with other antiangiogenic targeted therapies, hypertension, and bleeding were the most worrisome AEs. Here, we observed no fatal bleeding or hypertension, but only grade 3 hypertension in one patient. In addition, there were no new safety signals for additional anlotinib in combination with immunotherapy compared with anlotinib alone.

Some limitations of this study should be noted. First, data from a single center with relatively small sample sizes were analyzed retrospectively, which made patient selection bias difficult to avoid, and there was a lack of comparisons between anlotinib alone and anlotinib plus immunotherapy. Second, additional anlotinib and immunotherapy validated the synergistic effect rather than the survival benefit of anlotinib, although our data showed OS prolongation by comparing historical data from previous studies.

5 | CONCLUSION

In conclusion, anlotinib, and in particular the addition of immunotherapy to anlotinib, represents an effective add-on therapy for the second- or later-line treatment of PDAC with tolerable AEs. Anlotinib in combination with immunotherapy showed prolonged OS in patients with baseline RDW <14%. However, in the future, prospective studies with increased sample sizes and stepwise control groups are needed to further confirm our findings.

AUTHOR CONTRIBUTIONS

Boyu Qin: Conceptualization (equal); formal analysis (equal); methodology (equal); writing—original draft (lead). **Qi Xiong**: Conceptualization (equal); methodology (equal); writing—original draft (supporting). **Lingli Xin**: Conceptualization (equal); methodology (equal); writing—original draft (supporting). **Ke Li**: Data curation (equal); writing—review and editing draft (supporting). **Weiwei Shi**: Methodology (equal); writing—original draft (equal). **Qi Song**: Methodology (equal); writing—original draft (equal). **Qiong Sun**: Methodology (equal); writing—original draft (equal). **Jiakang Shao**: Formal analysis (equal); writing—original draft (supporting). **Jing Zhang**: Writing—original draft (supporting). **Xiao Zhao**: Formal analysis (equal); writing—original draft (supporting). **Jinyu Liu**: Data curation (equal); investigation (equal); writing—review and editing (lead). **Jinliang Wang**: Conceptualization (lead); formal analysis (equal); investigation (equal); writing—review and editing (equal). **Bo Yang**: Conceptualization (lead); investigation (equal); writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army (No. S2021-553-01) and was carried out in accordance with the principles of the Declaration of Helsinki. Given the retrospective nature of this study, informed consent was waived.

INFORMED CONSENT

Not applicable.

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