The efficacy and adverse events of anlotinib plus PD-1 inhibitor for metastatic solid tumors

Hao Lin
Department of Oncology, Huashan Hospital, Fudan University
Tao Liu
Department of Oncology, Huashan Hospital, Fudan University
Xinli Zhou (xinli_zhou73@163.com)
Department of Oncology, Huashan Hospital, Fudan University
Xiaohua Liang
Department of Oncology, Huashan Hospital, Fudan University

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Abstract

Background

Several antiangiogenic tyrosine kinase inhibitors (TKIs) have the potential to modulate the tumor immune microenvironment and improve immunotherapy effect Of these, anlotinib has demonstrated antitumor efficacy in clinical trials. However, its role in immune regulation and the potential synergistic antitumor effect of its combination with PD-1 inhibitor remain unclear. This study investigated the efficacy and adverse events (AEs) of the combination of anlotinib and PD-1 inhibitor for solid tumors in real-world settings.

Methods

This retrospective study included patients with metastatic solid tumors treated with anlotinib plus PD-1 inhibitor at Huashan hospital, Fudan University between October 1, 2018 and August 31, 2020. The objective response rate was assessed using the response evaluation criteria in solid tumors v1.1. Descriptive statistics were performed using the Kaplan–Meier method, and any AEs were noted.

Results

Partial response was achieved in 13 patients, and 8 patients showed stable disease, representing a response rate of 43.3% and a disease control rate of 70%. The median progression-free survival was 3.8 months. Although AEs were observed in 50% of patients, most of them were Grades 1–2 and well tolerated. The most common AEs were thrombocytopenia (16%), thromboembolic or hemorrhagic events (16%), and rash (13%).

Conclusions

Anlotinib plus PD-1 inhibitor is an alternative salvage treatment choice in metastatic solid tumors with Favorable efficacy and tolerable toxicities.

Background

Anlotinib is a multitargeted tyrosine kinase receptor inhibitor (TKI) that selectively inhibits the vascular endothelial growth factor receptor(VEGFR), fibroblast growth factor receptor(FGFR), platelet-derived growth factor receptor (PDGFR) α and β, c-KIT[1]. Anlotinib exhibits activity against a broad range of malignancies such as non-small-cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC), gastric cancer (GC), colorectal cancer (CRC), medullary thyroid cancer, renal cell carcinoma (RCC), and soft tissue sarcoma[2].

Increasing evidence has exhibited the beneficial effects of antiangiogenic treatment on tumor growth and reprogramming of the immunosuppressive tumor microenvironment[3]. In preclinical models, the combination of antiangiogenic treatment with anti-PD1 immune checkpoint inhibitor (ICIs) stimulates the antitumor T cell response[4, 5], reduces immune suppressor cells[6, 7].

In a phase I clinical trial for squamous cell NSCLC, the combination of nivolumab and bevacizumab demonstrated a median progression-free survival (PFS) of 37.1 weeks, whereas nivolumab monotherapy exhibited a median PFS of 16 weeks[8]. Anlotinib is a multitargeted antiangiogenic TKI which have more superior efficacy than bevacizumab when combined with anti-PD1 ICIs. In a study presented at the World Conference on Lung Cancer in 2019, anlotinib combined with sintilimab (a PD-1 inhibitor) was used as a first-line treatment for NSCLC from a multicohort phase Ib trial and exhibited an objective response rate (ORR) of more than 60% regardless of different PD-L1 expression levels[9]. Anlotinib plus nivolumab exhibited a complete response (CR) in advanced ESCC[10]. Several ongoing clinical trials of immune therapy combined with anlotinib from ClinicalTrials.gov exhibit the studies of anlotinib combined with anti-PD1 ICIs in the treatment of soft tissue sarcoma, GC, NSCLC/SCLC, CRC, and endometrial cancer.

The data on the efficacy of anlotinib plus PD-1 inhibitor are preliminary but promising[11]. However, several challenges are present for the optimal treatment with anlotinib plus PD-1 inhibitor. The present study analyzed the efficacy and adverse events (AEs) of anlotinib combined PD-1 inhibitor in patients with metastatic solid tumors in a clinical setting.

Methods

Study design and patients

This retrospective study was conducted in patients with metastatic solid tumors treated with anlotinib plus PD-1 inhibitor in Huashan hospital, Fudan University from October 1, 2018, to August 31, 2020. Patients with metastatic solid tumors (including lung cancer, GC, cholangiocarcinoma, pancreatic cancer, CRC, and sarcoma confirmed by histological and cytological examination) who were treated with anlotinib plus PD-1 inhibitor such as toripalimab, nivolumab, pembrolizumab, or camrelizumab. Patients with organ disfunction (abnormal hematologic parameters, serum creatinine levels, and cardiac function, and LVEF $\leq$ 55%) and evidence of active infection were excluded from the study. The experiments were conducted in accordance with the Declaration of Helsinki. This was approved by the Ethics Committee of the Huashan Hospital, Fudan University. The requirement of informed consent was waived due to the retrospective nature of the study.

Treatments

Pre-treatment assessments included physical examination, bone scan, magnetic resonance imaging of the brain, and computed tomography (CT) scans of the chest, abdomen, and pelvis. All patients were administered oral anlotinib (supplied by Chia Tai Tiangqing Pharmaceutical Group Co., Ltd) (12 mg/day, 2 weeks on treatment and 1 week off treatment, 3 weeks per cycle) plus PD-1 inhibitor (intravenous

injection toripalimab 240 mg, 2 weeks per cycle, supplied by Junshi Biosciences Co., Ltd, China; or intravenous injection nivolumab 3 mg/kg, 2 weeks per cycle, supplied by Bristol-Myers Squibb, USA; or intravenous injection pembrolizumab 200 mg, 3 weeks per cycle, supplied by Merck Sharp & Dohme Corp, USA; or intravenous injection camrelizumab 200 mg, 2 weeks per cycle, supplied by Jiangsu Hengrui Medicine Co., Ltd, China).

Clinical data collection

Tumors were measured on CT scans based on the response evaluation criteria in solid tumors version 1.1 (RECIST v1.1) every 6 weeks for the first 6 months, and re-examined every 9 weeks thereafter.

Demographic characteristics such as sex, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), cancer types, central nervous system metastasis, and treatment history were collected. Additionally, at least one measurable radiographic response assessment was provided by two radiologists independently.

Definitions and follow up

PFS was defined as the time from the beginning of anlotinib plus PD-1 inhibitor to tumor progression or patient death. The disease control rate (DCR) was defined as the total percentage of patients with stable disease (SD), partial response (PR), and CR. ORR was defined as the total percentage of patients with PR and CR. Treatment-related AEs were captured according to the Common Terminology Criteria for Adverse Events 4.0.

Statistical analysis

All statistical analyses were performed using SPSS 25.0 (IBM Co. Armonk, NY, USA). Continuous variables were described as medians (minimum, maximum). Categorical variables were described as numbers (percentages). Survival analyses were performed using the Kaplan–Meier method. The descriptive variables regarding AEs and patient characteristics were directly calculated from the Huashan hospital health information system.

Results

Baseline characteristics

Of the 30 patients, 25 patients (83%) were male. The median age of the patients was 58 (range19-78) years. All patients had stage IV tumor disease. Of these, 20 patients (66.6%) had previous second-line treatments, and 13 (43.3%) with brain metastasis. Nine patients (30%) had received previous antiangiogenesis treatment, 5 patients received anlotinib, 3 patients received bevacizumab, 2 patients received apatinib, 10 patients (33.3%) received PD-1 inhibitor(8 patients received nivolumab, and 2 patients received pembrolizumab). The detailed demographic characteristic of these patients are presented in Table 1.

Table 1
Demographic characteristics

characteristics		Patients (n = 30)	Percentage (%)
Age (years), median (range)		58 (35–70)	/
Sex	Male	25	83
	Female	5	7
ECOG PS	0–1	17	57
	≥ 2	13	43
Tumor types	NSCLC	7	23
	SCLC	7	23
	ICC	4	14
	SC	3	10
	CRC	1	3
	NEN	1	3
	STS	2	7
	HCC	1	3
	LELC	1	3
	ACC	1	3
	CUP	1	3
	Paget's	1	3
Brain metastases	Yes	13	43
	No	17	57
Previous treatment lines	≤ 2	10	33
	> 2	20	67
PD-1 inhibitor	Toripalimab	21	70
	Nivolumab	4	13

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small-cell lung carcinoma; SCLC, small-cell lung carcinoma; ICC, intrahepatic cholangiocarcinoma; SC, stomach cancer; CRC, colorectal cancer; NEN, neuroendocrine neoplasm,; STS, soft tissue sarcoma; HCC, hepatocellular carcinoma; LELC, lymphoepithelioma-like carcinoma; ACC, adenoid cystic carcinoma; CUP, cancer of unknown primary; ICI, anti-PD1 immune checkpoint inhibitor.

characteristics		Patients (n = 30)	Percentage (%)
	Pembrolizumab	4	13
	Camrelizumab	1	4
Previous antiangiogenic treatment	Yes	9	30
	No	21	70
Previous PD-1 inhibitor treatment	Yes	10	33
	No	20	67

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small-cell lung carcinoma; SCLC, small-cell lung carcinoma; ICC, intrahepatic cholangiocarcinoma; SC, stomach cancer; CRC, colorectal cancer; NEN, neuroendocrine neoplasm,; STS, soft tissue sarcoma; HCC, hepatocellular carcinoma; LELC, lymphoepithelioma-like carcinoma; ACC, adenoid cystic carcinoma; CUP, cancer of unknown primary; ICI, anti-PD1 immune checkpoint inhibitor.

Efficacy

The median number of cycles administered to the 30 patients was 4.7 (range: 2–6) cycles. At the end time of November 10, 2020, 23 (76.6%) patients had disease progression. The overall DCR was 70%, and the median PFS was 3.8 months (Fig. 1). A total of 13 (43.3%) patients achieved PR and 8 (26.6%) achieved SD. The ORR for the histologic subtypes are presented in Table 2. The ORR for patients with brain metastasis was 53.8% (n = 7), whereas that for patients received previous two lines of treatments was 30% (n = 6). The ORR for patients with previous antiangiogenesis treatment was 22.2% (n = 2), whereas ORR for patients with previous PD-1 inhibitor was 30% (n = 3). At the time of analysis, 40% of patients (n = 12) died. The median overall survival (OS) was still not reached.

Table 2
The efficacy of different malignant disease treated with anlotinib and PD-1 inhibitor

Tumor type	Total (n = 30)			
	CR No. (%)	PR No. (%)	SD No. (%)	PD No. (%)
NSCLC	0 (0)	4 (57.1)	1 (14.2)	2 (28.5)
SCLC	0 (0)	5 (71)	1 (14.2)	1 (14.2)
ICC	0 (0)	2 (50)	0 (0)	1 (25)
SC	0 (0)	0 (0)	2 (66.6)	1 (33.3)
CRC	0 (0)	0 (0)	0 (0)	1 (100)
NEN	0 (0)	1 (100)	0 (0)	0 (0)
STS	0 (0)	0 (0)	1 (50)	1 (50)
HCC	0 (0)	1 (100)	0 (0)	0 (0)
LELC	0 (0)	0 (0)	1 (100)	0 (0)
ACC	0 (0)	0 (0)	0 (0)	1 (100)
CUP	0 (0)	0 (0)	1 (100)	0 (0)
Paget's	0 (0)	0 (0)	1 (100)	0 (0)
Total	0 (0)	13 (43.3)	8 (26.2)	9 (30)

Abbreviations: NSCLC, non-small-cell lung carcinoma; SCLC, small-cell lung carcinoma; ICC, intrahepatic cholangiocarcinoma; SC, stomach cancer; CRC, colorectal cancer; NEN, neuroendocrine neoplasm; STS, soft tissue sarcoma; HCC, hepatocellular carcinoma; LELC, lymphoepithelioma-like carcinoma; ACC, adenoid cystic carcinoma; CUP, cancer of unknown primary.

Adverse events

Of the 30 patients, all therapy-related AEs (Grades 1–4), including fatigue (33.3%), diarrhea (16.6%), thrombocytopenia (16.6%), rash (13.3%), thromboembolic events (10%), hand–foot skin reaction (10%), hemorrhagic (6.6%), alanine aminotransferase (ALT) elevation (6.6%), aspartate aminotransferase (AST) elevation (6.6%), and interstitial lung disease (3.3%) were reported in 15 (50%) patients. The most frequently reported AEs of ≥ Grade 3 were thrombocytopenia (16.6%), fatigue (10%), thromboembolic events (3.3%), and rash (3.3%). A total of 9 (30%) patients stopped treatment with anlotinib due to side effects. No therapy-related deaths were noted (Table 3).

Table 3
Adverse events(n = 30)

	Total No. (%)	≥Grade III No. (%)
Leukopenia	3 (10)	0 (0)
Thrombocytopenia	5 (16.6)	5 (16.6)
Thromboembolic	3 (10)	1 (3.3)
Hemorrhagic	2 (6.6)	0 (0)
Rash	4 (13.3)	1 (3.3)
Interstitial lung disease	(3.3)	0 (0)
Diarrhea	5 (16.6)	0 (0)
Hand–foot skin reaction	3 (10)	0 (0)
ALT elevation	2 (6.6)	0 (0)
AST elevation	2 (6.6)	0 (0)
Fatigue	10 (33.3)	3 (10)
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.		

Discussion

Anlotinib, a newly developed oral antiangiogenic TKI, has exhibited the combination efficacy with PD-1inhibitor in preclinical models[12]. As we know, the present study is the first series analysis to evaluate the therapeutic effect and AEs for the combination of anlotinib and PD-1inhibitor for metastatic solid tumors such as NSCLC, SCLC, SC, and ICC.

Of the 30 patients, 66.6% patients had previous second-line treatments, whereas 43.3% patients had brain metastasis. The results showed adequate disease control in the treatment of different metastatic solid tumors. The DCR and ORR was 70% and 43.3%, respectively. The ORR for SCLC was 71%, for NSCLC was 57.1%, and ICC was 50%. Additionally, ORR for patients with brain metastasis was up to 53.8%. PD-1inhibitor alone could improve overall survival time than placebo in second- or later-line treatment for NSCLC and GC. However, the ORR for NSCLC and GC was only 16.6%[13] and 11.6%[14], respectively. Anlotinib also had clinical activity in NSCLC and GC; however, the ORRs were only 9.2%[15] and 4.9%[16], respectively. Our study revealed more favorable efficacy of this combination than those of single agents in other studies.

The toxicities of anlotinib or PD-1inhibitor were tolerable and manageable in clinical trials and real-world[17–19], and the fatal complications associated with ICI was uncommon. However, the AEs associated with this combination are unclear and have not yet been investigated. In a study presented at

American Society of Clinical Oncology in 2019, camrelizumab combined with apatinib was used in the first-line treatment for NSCLC. The ORR and DCR in this study were 29.7% and 81.3%, respectively. However, 56.2% of patients had ≥ Grade 3 therapy-related AEs[20]. The Checkmate 016 evaluated the clinical activity of the combination of nivolumab with sunitinib or pazopanib in the patients with metastatic RCC. Thirty-three patients received nivolumab and sunitinib, 19 of whom were treatment-naïve. The ORR of these patients was 55%, whereas PFS was 12.7 months. Twenty patients received nivolumab and pazopanib, who had ≥ 1 prior systemic therapy. The ORR of these patients was 45%, whereas PFS was 7.2 months. However, the addition of standard doses of sunitinib or pazopanib to nivolumab resulted in high incidence of ≥ Grade 3 therapy-related AEs (82% and 70%, respectively)[21]. Axitinib is a more selective VEGF inhibitor[22]. Thus, it could be combined safely with pembrolizumab and exhibit adequate antitumor activity in patients with treatment-naïve advanced RCC[23]. Although ORR was 73%, 54% patients had therapy-related serious AEs[24].

Lower doses are superior to higher doses for eliciting a relatively immune-supportive tumor microenvironment and reengineering the tumor microenvironment for active immunotherapies in the clinical setting. This is supported by the data from the phase Ib trial REGONIVO.[20] This study evaluated the treatment effect of the combination of regorafenib and nivolumab for GC and CRC. Regorafenib 160 mg was associated with three dose-limiting toxicities (DLTs). However, no DLTs were observed with 120 or 80 mg regorafenib. The ORR was 45.5% with 80 mg regorafenib and 36.0% with 120 mg regorafenib[25]. The intolerable toxicities of PD-1inhibitor combined with antiangiogenic TKIs obstacled the further clinical research. Evidence indicates that the favorable efficacy of combination of PD-1inhibitor and antiangiogenic TKIs may be dependent on careful selection of TKIs and the dosage.

The present study evaluated the adverse events of anlotinib plus PD-1inhibitor for solid tumors. The toxicity profiles are consistent with those of antiangiogenic TKIs or PD-1inhibitor in other studies. Although AEs appeared in 50% of patients in the present study, most were of Grades 1–2. The combination treatment was generally well tolerated. The most common therapy-related AE was fatigue (33.3%), whereas the most common ≥ Grade 3 therapy-related AE was thrombocytopenia (16.6%). Treatment was stopped in 30% of patients on anlotinib due to side effects. However, no therapy-related deaths occurred. Hematotoxicity was a common toxicity associated with this combination suggesting immune-mediated events associated with this combination. Thrombocytopenia was observed in 16% of patients, the severity of which was beyond Grade 3. Additionally, 16% of patients experienced thromboembolic or hemorrhagic events. Therefore, the anlotinib dosage should be reduced from 12 mg to 10 mg in future studies.

The small sample size was the major limitation of our study. Thus, the analysis of the treatment effect was preliminary in nature. Most patients had superior ECOG PS despite had several lines of chemotherapy. Antitumor response was observed in patients with NSCLC and SCLC, the efficacy of other tumor patients was not statasticly evaluated because of the small sample size.

Therefore, the combination of anlotinib and PD-1inhibitor demonstrated a favorable efficacy and tolerable toxicities in patients with solid tumors, which can provide an alternative salvage therapy for such patients.

List Of Abbreviations

ICIs, immune checkpoint inhibitors;

TKI, tyrosine kinase inhibitor

AEs, adverse events

MET, mesenchymal epithelial transition

CR, complete response

CRC, colorectal cancer

CT, computed tomography

DCR, disease control rate

DLTs, dose-limiting toxicities

ESCC, esophageal squamous cell carcinoma

GC, gastric cancer

NSCLC, non-small-cell lung cancer

ORR, objective response rate

OS, overall survival

PDGFR, platelet-derived growth factor receptor

PFS, progression-free survival

PR, partial response

RCC, renal cell carcinoma

SD, stable disease

VEGF, vascular endothelial growth factor

ALT, alanine aminotransferase

AST, aspartate aminotransferase

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Declarations

Ethics approval and consent to participate

The experiments were conducted in accordance with the Declaration of Helsinki. This was approved by the Ethics Committee of the Huashan Hospital, Fudan University. The requirement of informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and materials

The data set supporting the results of this article are included within the article.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

Xiaohua Liang, Xinli Zhou, Hao Lin conceived and coordinated the study, designed, performed and analyzed the experiments, wrote the paper. Xiaohua Liang, Hao Lin and Tao Liu carried out the data collection, data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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Figures

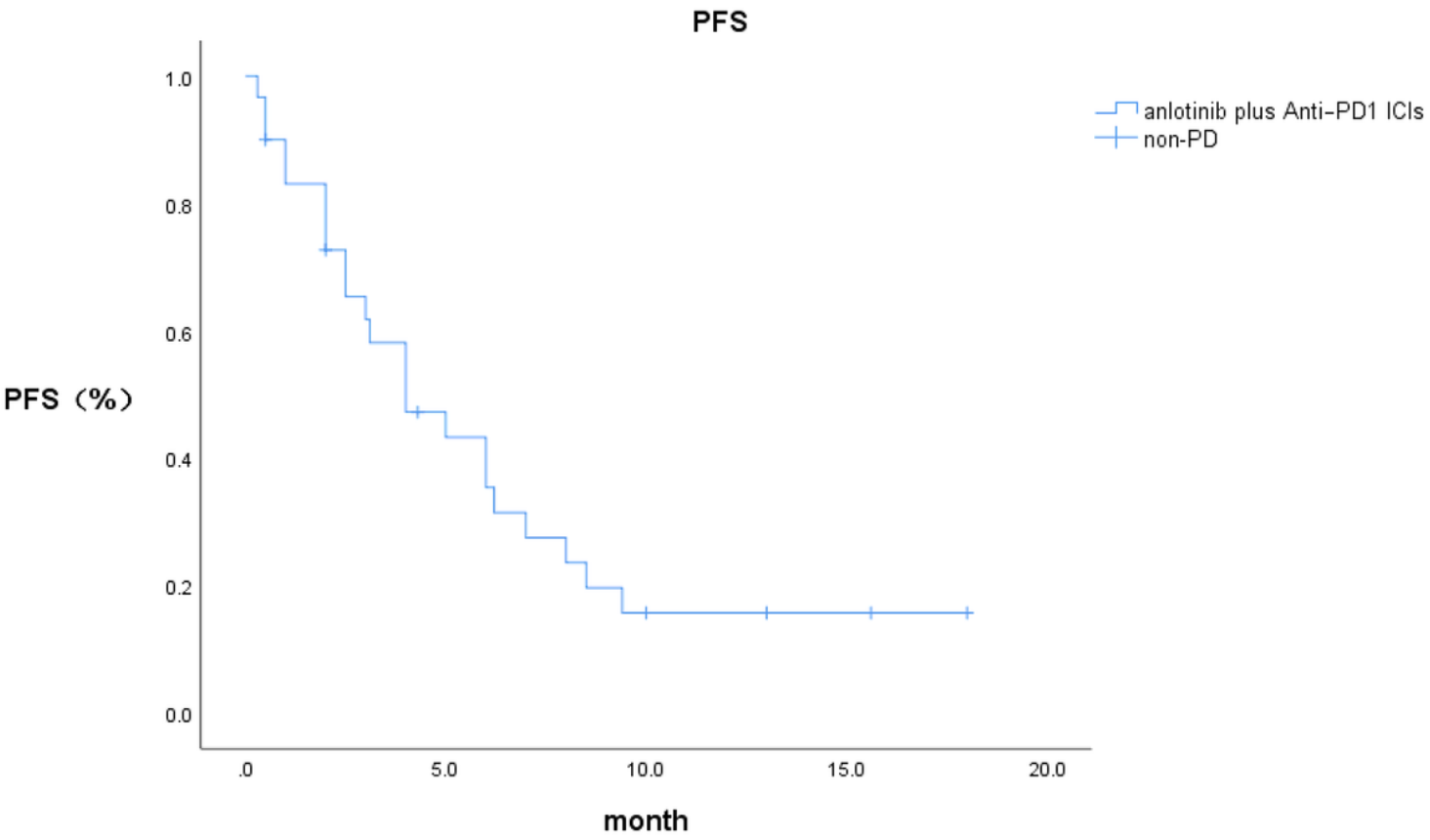

Figure 1

PFS of 30 patients treated with anlotinib plus PD-1 inhibitor