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ORIGINAL ARTICLE

Efficacy and safety of anlotinib in patients with advanced malignancy: a single-center, single-arm, phase 2 trial

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Abstract

Background For advanced tumors that lack specific oncogenic alteration and are resistant to chemotherapy, anti-angiogenesis therapy or immunotherapy or a combination of the two are the most important treatments. Anlotinib is a newly developed oral small molecule receptor tyrosine kinases inhibitor with the potency of inhibiting tumor angiogenesis. This was an open-label, single-arm, phase 2 study to validate the efficacy and safety of anlotinib in patients with various cancer types.

Methods Patients with advanced malignancy who have failed previous therapies or lack effective treatment choices received daily oral administration of 12 mg anlotinib on days 1–14 every 3 weeks until disease progression, intolerable toxicity or physician decision. The primary endpoint was objective response rate (ORR).

Results A total of 93 eligible patients with 26 different cancer types were enrolled. The overall ORR was 21.5%. The median PFS was 5.7 months and median OS was 12.0 months. The most common treatment-related AE of all grades and of grade 3 was both hypertriglyceridemia at an incidence of 40.9% and 5.4%, respectively.

Conclusions Anlotinib exhibits objective efficacy and safety in advanced malignancy and might be a possible treatment option for many types of cancer patients who have failed prior treatment and with no optimal therapy regimen.

Keywords Anlotinib · Advanced malignancies · Objective response rate · Progression-free survival · Safety

Introduction

Receptor tyrosine kinases (RTKs) are key transmembrane glycoproteins that play important roles in intracellular tyrosine phosphorylation and intracellular signaling, controlling various physiological cancerogenesis processes such as cell proliferation, differentiation, metabolism, and apoptosis [1], as well as functions in "tumor microenvironment" cells such as angiogenesis [2]. Targeting tyrosine kinases receptors is one of the most important and promising strategy in cancer treatment [3]. Since the tumor development is involved in various signal pathways and tyrosine kinases receptors, multikinase inhibitors (MKIs) may provide more efficiency and be less vulnerable to adaptive resistance [4]. In the last decade, the success of sorafenib, sunitinib, pazopanib, cabozantinib and other MKIs has confirmed this assumption [5–8].

Anlotinib is a newly developed oral small molecule receptor tyrosine kinases inhibitor with the potency of inhibiting tumor angiogenesis as well as cell proliferation simultaneously and have been approved to treat advanced non-small cell lung cancer (NSCLC) in China [9]. In vitro studies, anlotinib selectively inhibited VEGFR2 with an IC_{50} value of 0.2 nM, 20 times as potent as sunitinib [10]. Anlotnib also binds to FGFR and PDGFR to overcome the bypass activation induced by the inhibition of VEGFR [11]. Another key mechanism for its anti-tumor activity is the inhibition of c-Kit, which binding stem cell factor (SCF) and playing an important role in cell survival, proliferation, and differentiation [12].

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Due to the potency of simultaneously inhibiting multiple signaling pathways involved in tumor cell proliferation and angiogenesis, which are the general characteristics for various solid tumors despite of different etiology and cellular mutations, multi-target TKIs have a theoretically "broad spectrum" applications in cancer treatment [13]. For patients who have failed in standard treatment, and those without a proper choice of treatment regimen, MKI agents provided a practical choice. In previous phase I trial, anlotinib has showed a good response in a variety of cancer types besides of NSCLC [14]. We performed a phase 2 study to further validate the efficacy of anlotinib in patients with refractory tumors.

Materials and methods

Study design

This was an open-label, single-center, single-arm, phase 2 study to explore the efficacy and safety of anlotinib in patients with advanced malignancy who failed in standard treatment or lack a proper treatment regimen. Eligible patients were administrated anlotinib 12 mg orally once daily on days 1–14 every 3 weeks. Treatment was continued until disease progression (RECIST 1.1), unacceptable toxicity (NCI CTCAE), withdrawal of consent or considered to be unsuitable for continued treatment by the investigator. Efficacy (indicated by treatment response) and safety outcomes were evaluated every 2 treatment cycles.

This study was conducted in accordance with the Declaration of Helsinki and with the approval of institutional review board. All patients provided written informed consent.

Patients

Patients were recruited in our hospital. Eligible patients were aged 18–70 years, diagnosed with advanced malignancy and were considered to be with no effective treatment choice, including those who have failed conventional treatment.

The studied malignancies included digestive tract tumors, gynecological-related tumors, breast cancer, melanoma, and gastrointestinal stromal tumors. All enrolled patients had an Eastern Cooperative Oncology Group performance status score $0 \sim 1$, expected survival ≥ 3 months, no pregnancy, and no severe abnormalities in laboratory tests. Patients who received chemotherapeutic therapy were not enrolled until the treatment has been discontinued for at least 30 days (at least 6 weeks for nitrosourea and mitomycin C). Patients who underwent major surgery were not enrolled until at least 4 weeks after the surgery date.

Exclusion criteria included: other malignant tumors or history besides the primary diagnosis (except for cured skin basal cell carcinoma or in situ cervical carcinoma); difficulties in oral medications; brain metastasis, spinal cord compression, cancerous meningitis; previously NCI CTC AE grade > 1 toxicity in previous therapy; Severe and/or uncontrolled diseases; myocardial ischemia or; active or uncontrolled serious infections; other liver diseases; poorly controlled diabetes control; long-term unhealed wounds or fractures; bleeding tendency or treated with anticoagulants or vitamin K antagonists; history of psychotropic substance abuse or mental disorder; history of immunodeficiency, including HIV positive or other acquired, congenital immunodeficiency disease, or a history of organ transplantation.

Treatment regimen

During each treatment cycle, eligible patients were administrated anlotinib at a dosage of 12 mg orally once daily on days 1–14 every 3 weeks. Treatment would be suspended if CTC AE degree 3 non-hematologic toxicity or degree 4 hematologic toxicity occurred. Treatment would be resumed at dosage of 10 mg/day if the degree of adverse reactions decreased to less than degree 2 in two weeks. Otherwise the treatment would be withdrawn. Treatment suspension and resumption followed the same rule of 2 week recovery for all subsequent AEs and toxicities. Treatment continued until disease progression (PD) or the patient was considered not suitable for continuous medication by the investigator.

No other anti-tumor treatments were allowed until PD. Other medications were evaluated by the investigators before administration for safety and interferences with the study outcomes.

Efficacy outcomes

The primary efficacy outcome was objective response rate (ORR) during the first 6 treatment cycles, calculated as the percentage of patients with complete response (CR) or partial response (PR) according to the standards of RECIST 1.1. The secondary efficacy outcomes included disease control rate (percentage of patients with CR, PR and SD), progression-free survival (PFS) and overall survival (OS), which was calculated from the date of enrollment.

Safety outcomes

Occurrences and severity of adverse events were assessed in accordance with the Common Toxicity Standards of the National Cancer Institute (CTC AE4.0), and any adverse events that occurred within 1 month of the end of treatment, regardless of whether it was drug related, were included.

Statistical analysis

Efficacy outcomes were assessed in a full analysis set (FAS), defined as total number of patients who received ≥ 1 experimental drug administration. Outcome data of participants with early withdrawn due to reasons other than PD were filled in based on last observation carried forward (LOCF) method.

Safety outcomes were assessed in safety analysis set (SAS), defined as participants with at least 1 administration of experimental drug and a complete safety assessment record.

Descriptive statistics were used to analyze baseline characteristics and ORR. PFS and OS were summarized with the Kaplan–Meier method. Measurement data were statistically described using mean ± standard deviation or median (minimum, maximum), with 95% confidence interval calculated. The categorical data was statistically described using the frequency (percentage). All statistical analysis was performed using SAS 9.2 statistical analysis software.

Results and discussion

Patient characteristics

From August 2013 to August 2014, a total of 93 eligible patients were enrolled. The patient baseline characteristics are listed in Table 1. The median age was 50 years. The patients were diagnosed with 26 different cancer types. The most common diagnosis was colorectal cancer, with total 31 patients. Other types with more than 5 participants were thyroid cancer (9 patients), soft tissue sarcoma (7 patients) and neuroendocrine tumor (9 patients). 81.7% patients had chemotherapy history, and 41.9% patients received previous radiotherapy. At the end of the study, 58 patients suffered from disease progression and 2 were dead for cancer during the treatment. 19 patients discontinued their treatment due to adverse events and other 4 patients were considered not suitable for continued medication by the investigator. 10 patients withdrew their consents. The median duration of treatment was 4.0 months (IQR: 2.1, 8.5).

Efficacy

The efficacy of anlotinib treatment is summarized in Table 2 and the Kaplan–Meier survival curve for OS and PFS were shown in Figs. 1 and 2. PR was observed in 20 patients and given an ORR of 21.5% in all tested patients. Treatment responses were observed regardless of tumor type. To patients with thyroid cancer and soft tissue sarcoma, the ORR were 55.6% and 14.3%, which is consistent with our previous study (56.9% and 13%) [15, 16]. The ORR of 9

Table 1 Baseline characteristics of patients

Demographics	
Median age (range), years	50 (21–70)
Gender, *n* (%)	
Male	56 (60.2)
Female	37 (39.8)
Clinical	
Diagnosis *n* (%)	
Colorectal cancer	31 (33.3)
Thyroid cancer	9 (9.7)
Neuroendocrine tumor	9 (9.7)
Soft tissue sarcoma	7 (7.5)
Lung cancer	4 (4.3)
Gastric cancer	4 (4.3)
Hepatobiliary carcinoma	3 (3.2)
Primitive neuroectodermal malignancy	3 (3.2)
Osteosarcoma	2 (2.2)
Prostate cancer	2 (2.2)
Chondrosarcoma	2 (2.2)
Kidney cancer	2 (2.2)
Gastrointestinal stromal tumor	2 (2.2)
Pulmonary sarcomatoid carcinoma	1 (1.1)
Melanoma	1 (1.1)
Parathyroid carcinoma	1 (1.1)
Borderline mucinous cystadenoma	1 (1.1)
Skin squamous cell carcinoma	1 (1.1)
Breast cancer	1 (1.1)
Germ cell tumor	1 (1.1)
Esophageal cancer	1 (1.1)
Adenoid cystic carcinoma	1 (1.1)
Thymic carcinoma	1 (1.1)
Olfactory neuroblastoma	1 (1.1)
Right posterior mediastinum, chest wall malignancy	1 (1.1)
Primary liver cancer	1 (1.1)
ECOG score, *n* (%)	
0	86 (92.5)
1	7 (7.5)
Prior treatment, *n* (%)	
No	16 (17.2)
Yes	77 (82.8)
Prior chemotherapy, *n* (%)	
No	17 (18.3)
Yes	76 (81.7)
Prior radiotherapy, *n* (%)	
No	54 (58.1)
Yes	39 (41.9)
Other anti-tumor treatment history, *n* (%)	
No	59 (63.4)
Yes	34 (36.6)

ECOG Eastern Cooperative Oncology Group

Table 2 Efficacy of anlotinib treatment

	ORR (%)	DCR (%)	PFS (months); median (95% CI)	OS (months); median (95% CI)
Total ($N=93$)	21.5	79.6	5.7 (4.5, 8.4)	12.0 (8.9, 15.5)
Thyroid cancer ($N=9$)	55.6	77.8	22.8 (1.4, 40.1)	25.1 (1.9, -)
Colorectal cancer ($N=31$)	9.7	87.1	5.6 (4.0, 7.4)	9.4 (7.6, 12.9)
Soft tissue sarcoma ($N=7$)	14.3	57.1	6.0 (1.2, 10.9)	11.9 (2.5, 13.6)
Neuroendocrine tumor ($N=9$)	44.4	77.8	19.9 (13.4, 29.1)	32.7 (1.0, 40.8)
Others ($N=37$)	18.9	78.4	5.4 (3.8, 12.0)	9.1 (5.9, 17.8)

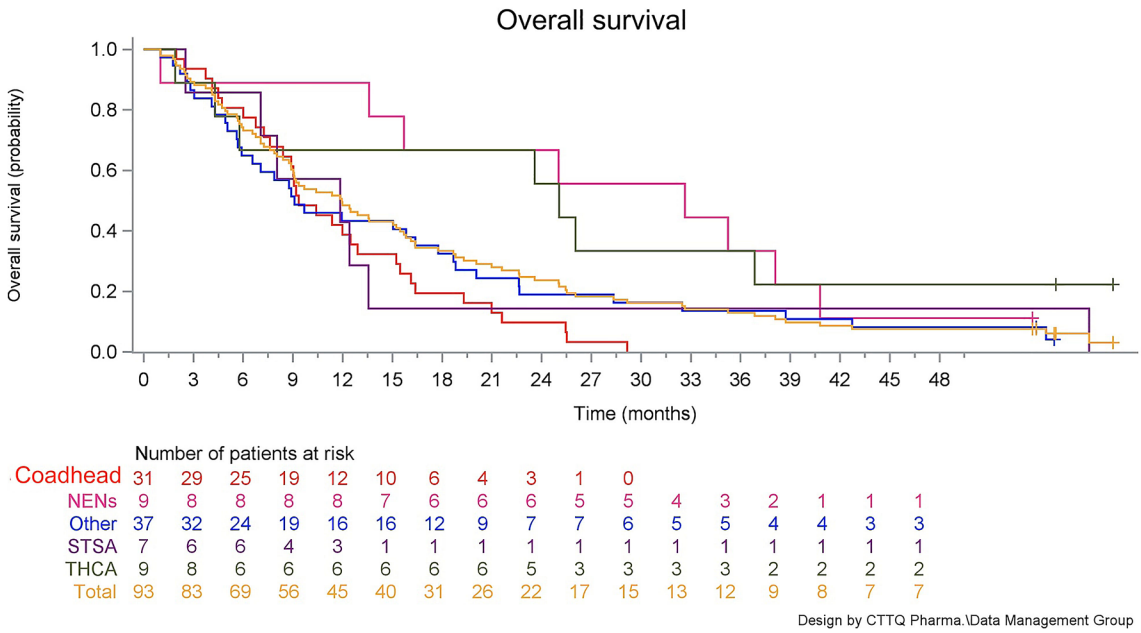

Fig. 1 Kaplan–Meier curve of overall survival

patients with neuroendocrine tumors was 44.4%. To colorectal cancer, which showed lower sensibility to VEGFR TKI monotherapy in previous study [17], treatment response was observed in 3 patients and given an ORR of 9.7%. More than half of patients underwent anlotinib treatment were observed disease stability and result in a disease control rate of 79.6% for all patients, which means most patients can benefit from anlotinib treatment. Especially, patients with colorectal cancer achieved an impressive high DCR of 87.1%.

The median follow-up time was 55.0 months (95% CI 53.6, 58.5). The median PFS and median OS were 5.7 months (95% CI 4.5, 8.4) and 12.0 months (95% CI 8.9, 15.5) for all patients, respectively. To 31 patients with colorectal cancer, the median PFS was 5.6 months (95% CI 4.0, 7.4) and median OS was 9.4 months (95% CI 7.6, 12.9). At the end of 12 and 24 months, 12 (38.7%) and 3 patients (9.7%) were still alive. Similar to the data of treatment response, the median PFS for patients with thyroid cancer (22.8 months) and soft tissue sarcoma (6.0 months) were also close to which we have reported [15, 16] although the sample size was small. The treatment response of anlotinib was durable and the median duration of response (DOR) was 16.0 months (95% CI 6.9, 27.9) for all patients. To 9 patients with thyroid cancer, an impressive long DOR of 38.3 months (95% CI 20.4, 38.3) was observed due to its sensibility to VEGF-TKI. On the other hand, although fewer patients achieved PR, 31 colorectal cancer patients still showed a DOR of 4.1 months (95% CI 4.1, 7.3).

Safety

Anlotinib treatment was safe and tolerable. Table 3 lists all treatment-related AEs occurring in > 10% patients. Treatment-related AEs of all grades were observed for nearly all patients (95.7%); however, the incidence of Grade 3 was 16.1% and Grade 4 was only 2.2%. The most common treatment-related

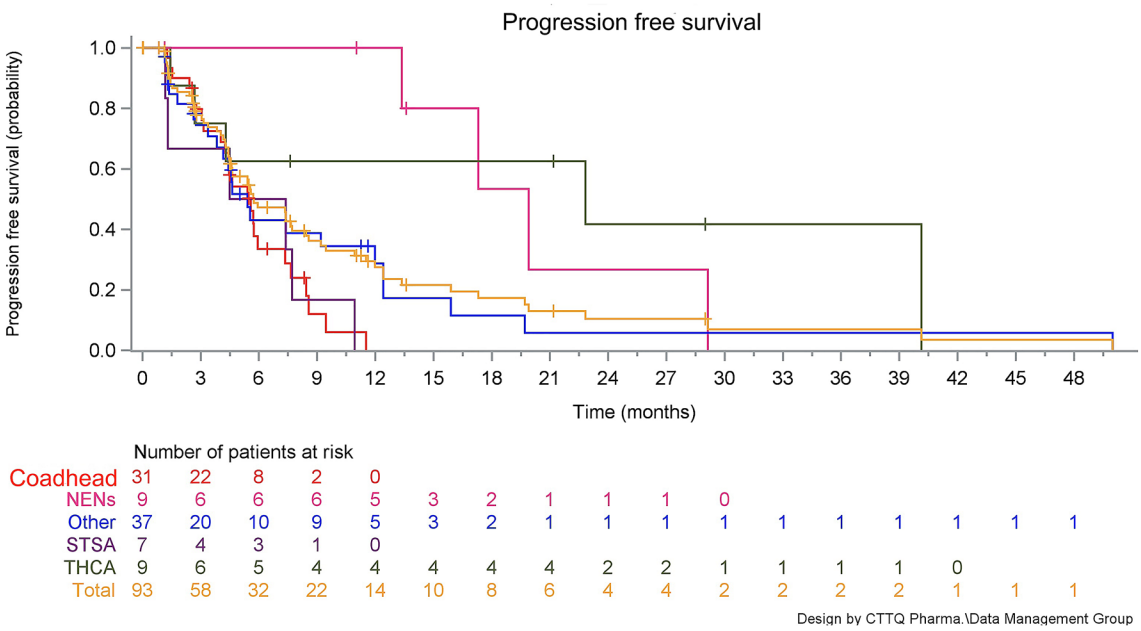

Fig. 2 Kaplan–Meier curve of progression free survival

Table 3 Treatment-related adverse events occurring in > 10% patients

Types of adverse events	Grade 1/2, *n* (%)	Grade 3/4, *n* (%)	Total, *n* (%)
Hypertriglyceridemia	38 (40.9)	5 (5.4)	43 (46.2)
Palmar–plantar erythrodysesthesia	37 (39.8)	2 (2.2)	39 (41.9)
Hypertension	36 (38.7)	1 (1.1)	37 (39.8)
Fatigue	34 (36.6)	0 (0.0)	34 (36.6)
Proteinuria	32 (34.4)	1 (1.1)	33 (35.5)
Hypercholesterolemia	28 (30.1)	0 (0.0)	28 (30.1)
Elevated blood bilirubin	27 (29.0)	0 (0.0)	27 (29.0)
Alanine aminotransferase elevation	22 (23.7)	0 (0.0)	22 (23.7)
Aspartate aminotransferase elevation	21 (22.6)	0 (0.0)	21 (22.6)
Loss of appetite	19 (20.4)	0 (0.0)	19 (20.4)
Diarrhea	19 (20.4)	0 (0.0)	19 (20.4)
Leukopenia	18 (19.4)	0 (0.0)	18 (19.4)
Oropharynx pain	15 (16.1)	0 (0.0)	15 (16.1)
Neutropenia	14 (15.1)	1 (1.1)	15 (16.1)
Dysphonia	13 (14.0)	0 (0.0)	13 (14.0)
TSH elevation	10 (10.8)	0 (0.0)	10 (10.8)

AEs were hypertriglyceridemia (40.9%), palmar–plantar erythrodysesthesia syndrome (39.8%), hypertension (38.7%), fatigue (36.6%) and proteinuria (34.4%). Grade 3 hypertriglyceridemia arose in 5 patients (5.4%) and others grade 3 AEs were only reported in one or two patients. No fatal treatment-related AEs occurred during the study. Anlotinb treatment was with a relatively low occurrence rate and severity for hematological and hemorrhage events. Only 8 patients experienced bleeding events (including urine erythrocytes) and no one was sorted as grade 3 or 4. Hematological events arose in 49 patients, which containing 2 grade 3 thrombocytopenia and 1 grade 3 anemia. Total 16 patients underwent dosage reduction during the treatment.

Discussion

The results of this phase 2 trial showed that anlotinib had antitumor activity in various advanced solid tumors who have failed in previous therapy or lack an effective treatment

option with an 21.5% ORR and 5.7 months of PFS. In addition, anlotinib showed a favorable safety profile in the studied patients, with treatment-related grade 3/4 AEs reported in less than 20% of the patients, and only 17.2% patients underwent a dose reduction during treatment. These results indicate that anlotinib might be a practical option for various advanced solid tumors who lack treatment regimen in current clinical practice.

This study aimed to evaluate anlotinib as a treatment option for patients with advanced tumors who failed prior therapy or lack optional treatment regimen. As one of the most common malignancies and with a limited choice of drug treatment currently [18], colorectal cancer patients were the most include in this study. This might also be due to a higher incidence in China. The second most enrolled groups were thyroid cancer, neuroendocrine tumor and soft tissue sarcoma. Once these diseases are in advanced stages, there is no standard treatment plan, so it is necessary to conduct more research on treatment options. In addition, the total patient population included 26 different cancer types. Although multi-targeted TKIs have been studied in various types of malignancies, this study included the most variety of cancer patients.

Considering that more than 82% of patients had experienced failure therapy, an overall ORR of 21.5% appeared to indicate a significant treatment response to anlotinib. The highest ORR was observed in thyroid cancer, the 55.6% ORR and 22.8 months of PFS appeared to be consistent with our phase II trials in MTC patients, in which 56.9% ORR and 76.4% of PFS at 24 weeks were observed, demonstrating a significant efficacy of anlotinib against placebo [15]. In addition, the 14.3% ORR and 6.0 months PFS in STS patients were consistent with our previous study in this disease (13% ORR, 5.6 months of PFS) [16]. In colorectal cancer, the 9.7% ORR, the 87.1% DCR and 5.6 months of PFS were observed. In a phase I study of regorafenib reported 38 patients with heavily pretreated, advanced or metastatic CRC were inrolled, 1 patient achieved PR, 19 patients SD, ORR was 4% (1/27) and DCR was 74%(20/27) [19]. In addition, neuroendocrine tumor showed high response rate to anlotinib, considering the complexity of pathology and difficult treatment options of this disease, these results might suggest future scaled up studies of anlotinib [20]. All other types of specific cancer were with small number of patients in the current study. Nevertheless, a total of 18.9% ORR indicated potential efficacies of anlotinib in those various malignancy types.

Although targeted therapies are usually with less toxicities compared to cytotoxic chemotherapy, the general activities of TKIs in various cellular pathways may raise the possibility of adverse events. Fatigue, diarrhea, fatigue, hand–foot skin reaction, nausea, vomiting, decreased appetite, hypertension and weight loss have been reported to be among the most common AEs experienced with TKIs [21–23]. Angiogenesis inhibitors were reported to be with significantly increased hand–foot syndrome, diarrhea, and gastrointestinal (GI) [23]. The specific AE profiles are related to the pathogenetic mechanism of the disease, as well as the anti-tumor target of TKIs.

In our previous studies, anlotinib showed tolerable safety profiles with low percentage of SAEs, the main serious adverse effects associated with anlotinib treatment included hypertension, triglyceride elevation, hand–foot skin reaction, and lipase elevation [14]. Consistently, most AEs in the current study were mild, with most grade 3/4 AEs identified in laboratory metabolic and enzyme tests. Anlotinib is primarily metabolized by cytochrome P450-mediated hydroxylation and dealkylation. The oxidized metabolites were excreted directly into the bile or excreted after conjugation, mainly forming glucuronides. As reported for other TKIs, liver adverse events were with varied incidences (5–25%) which can progress to severe liver injury in a minority of patients [24]. Therefore, the liver adverse events might require more attention in clinical usage of this agent. A total of 19 patients discontinued their treatment due to adverse events. There are 4 patients who are definitely not related to treatment, including 2 patients with non-treatment-related deaths, 1 patient with pleural effusion, and 1 patient with paraplegia. The 7 patients who discontinued treatment are mainly related to the complications caused by the tumor itself, such as 1 patient with pleural effusion caused by lung metastasis, 2 deaths unlikely related to the treatment, 1 patient with hemoptysis due to lung metastasis, 1 patient with biliary obstruction, 1 patient with elevated total bilirubin (TBIL), and one patient had incomplete intestinal obstruction. 8 cases of deaths were related to treatment-related AEs (TRAEs), including 1 case of proteinuria, 1 case of right nasal bleeding, 1 case of acute coronary syndrome due to thrombosis, 2 cases of hypertension, 1 case of thrombosis, and 1 case of pneumothorax. The pneumothorax may be spontaneous caused by the regression of lung and subpleural lesions in tumor patients. Besides of bleeding, targeting VEGFR may also cause thrombosis, which was related to the vessel endothelial injury and the subsequent activation of cytokines.

Although the mechanism is still unclear, multi-target TKIs for treatment was suggested to be associated with cardiotoxicity, represented by hypertension as AEs, potentially worsen the well-being of the treated patients. In previous studies of various TKIs in progressive medullary thyroid cancer, one common AE was hypertension [26]. SAEs of hypertension had also been observed in our previous studies of MTC treated with anlotinib. In this study, hypertension occurred with a generally high rate (39.8%), but only 1 patient was with grade 3/4 hypertension. Close attention should be paid to hypertension and cardiotoxicity AEs in the clinical applications of anlotinib.

Oral adverse events are common in targeted cancer treatment, however, mostly tend to be mild and manageable [27]. In addition, gastrointestinal events have been reported most often in relative studies [28]. In this study, although gastrointestinal AEs were with high incidence, they were mostly mild. Hematotoxicity is the most concerned AEs in systematic cancer treatment. However, it is usually with more significance in treatment of hematological tumor [29]. There were 1 grade 3/4 neutropenia and 1 grade 3/4 anemia.

The current study was with certain limitations. First, although the efficacy outcomes were assessed, as a single-arm trial, there is no clear conclusion that the patients could benefit from anlotinib treatment. In addition, as the most cancer types had very limited sample size, it is not possible to evaluate the exact application scenario of anlotinib in clinical practice. The major achievement of the current study was to assess the general safety profile and potential response of various advanced malignancy to anlotinib.

Conclusion

In conclusion, anlotinib exhibits objective efficacy and safety in advanced malignancy and might be a possible treatment option for many types of cancer patients who have failed prior treatment and with no optimal therapy regimen.

Future perspective

With the improvement of drug development, more and more new drugs based on different mechanism will come out in near future, with an unprecedented speed. The original pattern of indication application, which using large scale phase III study to apply for only one indication, will meet the bottleneck of execution difficulties. As the system of real world evidences gradually established and with the help of real world evidences, the pilot study named in phase II, especially those close to the clinical situation, will bring more drugs to quick approval.

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Author contributions YC was involved in study concepts and design, experimental studies/data analysis and statistical analysis. GJ was involved in study concepts, design and literature research. JZ and WL participated in clinical studies and manuscript editing. HT, C and JW were involved in literature research and clinical studies. YY participated in experimental studies/data analysis and manuscript preparation. NW was involved in guarantor of integrity of the entire study. YS participated in experimental studies/data analysis. All authors had full access to all study data and had final responsibility for the decision to submit the manuscript for publication.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

Consent for publication All authors agreed with the publication.

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