Clinical Trials: Targeted Therapy

Clinical Cancer Research

Safety and Efficacy of Anlotinib, a Multikinase Angiogenesis Inhibitor, in Patients with Refractory Metastatic Soft-Tissue Sarcoma

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Abstract

Purpose: The prognosis for patients with refractory soft-tissue sarcoma (STS) is dismal. Anlotinib has previously shown antitumor activity on STS in preclinical and phase I studies.

Patients and Methods: Patients 18 years and older, progressing after anthracycline-based chemotherapy, naïve from angiogenesis inhibitors, with at least one measurable lesion according to RECIST 1.1, were enrolled. The main subtypes eligible were undifferentiated pleomorphic sarcoma (UPS), liposarcoma (LPS), leiomyosarcoma (LMS), synovial sarcoma (SS), fibrosarcoma (FS), alveolar soft-part sarcoma (ASPS), and clear cell sarcoma (CCS). Participants were treated with anlotinib. The primary endpoint was progression-free rate at 12 weeks ($PFR_{12\ weeks}$).

Results: A total of 166 patients were included in the final analysis. Overall, the $PFR_{12\ weeks}$ was 68%, and objective response rate was 13% (95% confidence interval, 7.6%–18%). The median progression-free survival (PFS) and overall survival (OS) were 5.6 and 12 months, respectively. The $PFR_{12\ weeks}$, median PFS and OS were: 58%, 4.1 and 11 months for UPS ($n = 19$); 63%, 5.6 and 13 months for LPS ($n = 13$); 75%, 11 and 15 months for LMS ($n = 26$); 75%, 7.7 and 12 months for SS ($n = 47$); 81%, 5.6 and 12 months for FS ($n = 18$); 77%, 21 and not reached for ASPS ($n = 13$); 54%, 11 and 16 months for CCS ($n = 7$); and 44%, 2.8 and 8.8 months for other sarcoma ($n = 23$), respectively. The most common clinically significant grade 3 or higher adverse events were hypertension (4.8%), triglyceride elevation (3.6%), and pneumothorax (2.4%). No treatment-related death occurred.

Conclusions: Anlotinib showed antitumor activity in several STS entities. The toxicity was manageable. *Clin Cancer Res; 24(21); 5233–8. ©2018 AACR.*

Introduction

Soft-tissue sarcoma (STS) represents a heterogeneous malignant tumor category comprising over 50 different entities that associated with distinct morbidity and mortality (1). For patients diagnosed with advanced or metastatic STS, doxorubicin alone or in combination with other cytotoxic agents has been typically recommended as the first-line treatment in the past four decades (2–6). Olaratumab, a recombinant monoclonal antibody against platelet-derived growth factor receptor α (PDGFRα), showed a highly significant improvement of OS when combined with doxorubicin, highlighting the potential of PDGFRα as a therapeutic target for STS (7). Also, several novel agents have been approved for the treatment of STS after failure of standard chemotherapy, including trabectedin for leiomyosarcoma (LMS) and liposarcoma (LPS; refs. 8, 9), eribulin for LPS (10), and pazopanib for nonadipocytic and nongastrointestinal stromal tumor (GIST) STS (11). However, the prognosis of patients with metastatic STS remains dismal, with a median OS barely exceeding 1 year (5, 12). This highlights an ongoing challenge with the relatively small increments of effective treatment and represents an unmet medical need warranting further investigation.

A number of comprehensive genomic analyses have identified specific molecular alterations in STS (13, 14). VEGF is one of the

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Currently, pazopanib is the only tyrosine kinase inhibitor (TKI) approved by FDA for nongastrointestinal stromal tumor and nonadipocytic soft-tissue sarcoma (STS) that progressed after standard chemotherapy. For Chinese STS patients who failed chemotherapy, there is no available standard drug as pazopanib has not been approved for treating STS in China. Anlotinib is a new TKI, inhibiting kinases involved in angiogenesis and tumor proliferation. In this phase II study, anlotinib showed antitumor activity in several STS subtypes that progressed after previous anthracycline-based chemotherapy. In contrast to pazopanib and regorafenib, anlotinib has shown clinical activity in liposarcoma highlighting the uniqueness of anlotinib. The toxicity was manageable and acceptable.

main drivers for angiogenesis, which plays a crucial role in tumor growth, invasion, and metastasis (15, 16). Besides, the dysregulation of FGF/FGFR axis promotes cancer progression and enhances the angiogenic potential of tumor microenvironment (17, 18). In addition to the angiogenic pathway, factors in proliferative pathway, such as PDGF and c-Kit, are also likely to contribute to the highly malignant phenotype of STS (19, 20). Taken together, these findings provide a rationale for proangiogenic and proliferative factors to serve as the potential targets for treatment of STS.

Anlotinib is a novel tyrosine kinase inhibitor targeting multiple factors involving tumor proliferation, vasculature, and tumor microenvironment (21). Anlotinib inhibits VEGF/VEGFR signaling by selectively targeting VEGFR-2,-3 and FGFR-1,-2,-3,-4 with high affinity. Anlotinib also suppresses the activity of PDGFRα/β, c-Kit, Ret, Aurora-B, c-FMS, and discoidin domain receptor 1 (DDR1), leading to significant inhibition of tumor proliferation (21). In the preclinical stage, anlotinib showed broad antitumor activity against a variety of xenograft models (21).

In phase I study, anlotinib showed promising antitumor potential against many types of tumor such as colon adenocarcinoma, non–small cell lung cancer, renal clear cell cancer, medullary thyroid carcinoma, and STS. Pharmacokinetic assessment indicated that anlotinib reached its maximum plasma concentration with T_{max} of 4 to 11 hours after dosing, and then it eliminated slowly with $t_{1/2}$ of 64 to 136 hours. The main serious adverse effects were hypertension, triglyceride elevation, hand–foot skin reaction, and lipase elevation (21).

Based on these promising results, the phase II study was designed to further investigate the antitumor effect of anlotinib on STS and assess the efficacy in different histologic subgroups. In addition, the tolerability was evaluated.

Patients and Methods

Study design and participants

This multicenter phase II study included patients from 15 institutions across China. Eligible patients were required to be 18 years or older, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, progress after anthracycline-based first-line chemotherapy, be naïve from antiangiogenic agents, and have at least one measurable lesion according to RECIST 1.1. Several histologic subtypes were allowed, including undifferentiated pleomorphic sarcoma (UPS), liposarcoma (LPS), leiomyosarcoma (LMS), synovial sarcoma (SS), fibrosarcoma (FS), alveolar soft-part sarcoma (ASPS), clear cell sarcoma (CCS), malignant peripheral nerve sheath tumor (MPNST), angiosarcoma, and epithelioid sarcoma. Patients with the following entities were excluded: GIST, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, dermatofibrosarcoma protuberans, Ewing sarcoma, primitive neuroectodermal tumor, inflammatory myofibroblastic tumor, and malignant mesothelioma. Pathology materials (tumor blocks or representative slides) were centrally reviewed.

The main exclusion criteria included prior treatment with antiangiogenic agents such as sunitinib, sorafenib, and bevacizumab, known history of or concomitant malignancy likely to affect life expectancy except curative skin basal cell carcinoma and cervical carcinoma *in situ*, chemotherapy or radiotherapy within 28 days before start study entry, taken part in other clinical trial within 28 days before study entry, ongoing toxicity > grade 2 according to Common Terminology Criteria for Adverse Events v4.0 (CTCAE), inability to swallow oral medications, known history of brain or meningeal metastasis, and spinal compression. The complete inclusion and exclusion criteria were in Supplementary Methods S1. The trial was registered at ClinicalTrials.gov (NCT01878448).

The protocol was approved by the Institutional Review Board at each participating institution center and complied with good clinical practice guidelines, as well as the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Procedures

After verification of eligibility criteria, patients would receive oral anlotinib 12 mg, once daily, 2-week on/1-week off, until disease progression according to RECIST 1.1, death, unacceptable toxicity, or withdrawal of consent for any reasons. A cycle was considered to be 3 weeks. During the treatment period, the tumor assessment would be done every 6 weeks. Dose modifications for adverse events were done according to the protocol. Clinical assessments of safety, including medical history and physical examination, and laboratory tests, were done every 3 weeks during the first 24 weeks and then at 6-week interval thereafter. Adverse events were graded according to CTCAE. All patients were followed up for survival (until death from any cause or withdrawal of consent). The primary endpoint was progression-free rate at 12 weeks ($PFR_{12\ weeks}$). Patients without progression who were alive at this time were considered to have treatment successes. Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response rate, disease control rate, and safety.

Statistical analysis

Allocation of a patient to a cohort was based on the diagnosis by the central pathologist. On the basis of a previous retrospective analysis, $PFR_{12\ weeks}$ associated with active and inactive second-line therapies in patients with advanced STS were determined as 40% and 20%, respectively (22, 23). A Simon, optimal, one-sample, two-stage testing procedure was applied to each cohort separately with the following hypotheses: Successes in 20% or fewer of the patient cases were considered insufficient and did not warrant additional investigation, and successes in 40% or more of the patient cases were sufficient to warrant additional investigation. Applying these hypotheses with type I error of 5% and type II error of 20% each ($\alpha = 0.05$, $\beta = 0.2$). On the basis of optimal

design principle, 3 patients without disease progression at 12 weeks within the first 13 patients would expand this cohort to 43 patients. If 12 of 43 patients did not progress at 12 weeks in this cohort, the result would be positive (24, 25). A surplus recruitment to a maximum of 4 patients was allowed to correct for ineligible or untreated patients. Each cohort was recruited and enrolled at the same time. SS cohort was the first to reach the goal of recruitment. After SS cohort met the number of patients required, the recruitment for other cohorts was terminated early, and the results were analyzed.

PFS was defined as time from treatment initiation to either first disease progression or death from any cause. Patients alive at the time of analysis were censored at the date of last disease assessment. OS was measured from the date of treatment initiation to the date of death (from any cause). PFS and OS were estimated by the Kaplan–Meier method in each stratum. The following patient populations would be considered in the final analyses. Full analysis set (FAS): All patients who were eligible and had received their allocated treatment (at least one dose of the study drug); per protocol set (PPS): All patients who were eligible and had received their allocated treatment at least 6 weeks with good compliance; safety analysis set (SAS): All patients who had received treatment (at least one dose of the study drug). Formal tests of hypotheses were performed for the FAS population. The final data analysis was carried out in July 2016.

Role of the funding source

This clinical trial was funded by the Jiangsu Chia-tai Tianqing Pharmaceutical Co., Ltd. The funders had no role in the study design, data collection, or analysis. The corresponding author had full access to the data and took final responsibility for the decision to submit for publication.

Results

Between May 2013 and May 2015, a total of 166 eligible patients were recruited to this study [SS (n = 47), LMS (n = 26), FS (n = 18), UPS (n = 19), LPS (n = 13), ASPS (n = 13), CCS (n = 7), and other sarcomas (n = 23)]. The sarcoma subtypes included in the cohort "other sarcomas" were undifferentiated sarcoma (n = 3), spindle cell lipoma (n = 3), epithelioid sarcoma (n = 6), desmoplastic small round cell tumor (n = 1), malignant peripheral nerve sheath tumor (n = 4), embryonal sarcoma (n = 1), fibroblastoma (n = 1), and angiosarcoma (n = 4).

Table 1 shows demographics and patient baseline characteristics. The median age was 45.5 years old. A total of 94% patients had surgical history, and 41% patients received previous radiotherapy. A total of 7 patients, who were not eligible, were still included in the study (1 patient was 15 years old, 5 patients did not receive chemotherapy previously, and 1 patient was recorded as ECOG score of 3). All the inclusion was approved by the Institutional Review Board.

All patients started treatment according to protocol. Twelve patients were excluded from the PPS. Nine of the 12 patients retreated from the study within 6 weeks. Two were due to lack of target lesions according to RECIST 1.1, and the last patient was exposed to chemotherapy within 4 weeks before study entry. Therefore, 166 patients were subsumed in FAS and SAS, and 154 patients in PPS. The median follow-up was 6 cycles (4.2 months). At the time of analysis, 21 patients were still undergoing treatment, whereas 145 patients discontinued. The reasons for discontinuation included disease progression (n = 103), adverse events (n = 12), reasons unrelated to adverse events (n = 16), lost to follow-up (n = 3), withdraw of informed consent (n = 3), intercurrent death (n = 7), and protocol violation (n = 1).

Table 1. Patient demographics and clinical characteristics

Characteristics	Patients (FAS) *N* (%)	Patients (initial 43) *N* (%)	Patients (subsequent 123) *N* (%)
Age (years)			
Median	45.5	44	46
Range	18–70	18–70	18–70
Sex			
Male	100 (60)	29 (67)	71 (58)
Female	66 (40)	14 (33)	52 (42)
ECOG PS			
0	50 (30)	11 (26)	39 (32)
1	96 (58)	30 (70)	66 (54)
2	19 (11)	2 (5)	17 (14)
3	1 (1)	0 (0)	1 (1)
Histology			
SS	47 (28)	10 (23)	37 (30)
LMS	26 (16)	9 (21)	17 (14)
FS	18 (11)	2 (5)	16 (13)
UPS	19 (11)	3 (7)	16 (13)
LPS	13 (8)	3 (7)	10 (8)
ASPS	13 (8)	3 (7)	10 (8)
CCS	7 (4)	1 (2)	6 (5)
Other types	23 (14)	12 (28)	11 (9)
Radiotherapy history			
Yes	68 (41)	21 (49)	47 (38)
No	98 (50)	22 (51)	76 (62)
Surgery history			
Yes	156 (94)	41 (95)	115 (93)
No	10 (6)	2 (5)	8 (7)
Chemotherapy history			
Yes	161 (97)	42 (98)	119 (97)
No	5 (3)	1 (2)	4 (3)
Other antitumor therapy			
Yes	40 (24)	9 (21)	31 (25)
No	126 (76)	34 (79)	92 (75)

Efficacy

The primary endpoint $PFR_{12\ weeks}$ was 68%, and the median PFS was 5.6 months [95% confidence interval (CI), 4.4–7.7; Fig. 1A; Table 2]. For each cohort, the $PFR_{12\ weeks}$ and median PFS were: 58% and 4.1 months for UPS; 63% and 5.6 months for LPS, 75% and 11 months for LMS, 75% and 7.7 months for SS; 81% and 5.6 months for FS; 77% and 21 months for ASPS; 54% and 11 months for CCS; and 44% and 2.8 months for other sarcoma. The $PFR_{12\ weeks}$ was 53% and 73%, respectively, for the initial 43 and subsequent 123 patients enrolled during the study (Table 2). The median PFS was 5.3 months and 6.2 months, respectively, for the initial 43 and subsequent 123 patients (Table 2; Supplementary Fig. S1A).

The median OS was 12 months (95% CI, 11–16; Fig. 1B; Table 2). For each cohort, it was 11 months for UPS; 13 months for LPS; 15 months for LMS; 12 months for SS; 12 months for FS; 16 months for CCS; and 8.8 months for other sarcoma. Median OS has not been reached in the ASPS group. Approximately one third of patients experienced durable benefit from anlotinib treatment: 37% of patients were PFS free at 36 weeks, and 32% of patients survived more than 24 months (Table 2). The median OS was 9.9 and 13 months, respectively, for the initial 43 and subsequent 123 patients (Table 2; Supplementary Fig. S1B).

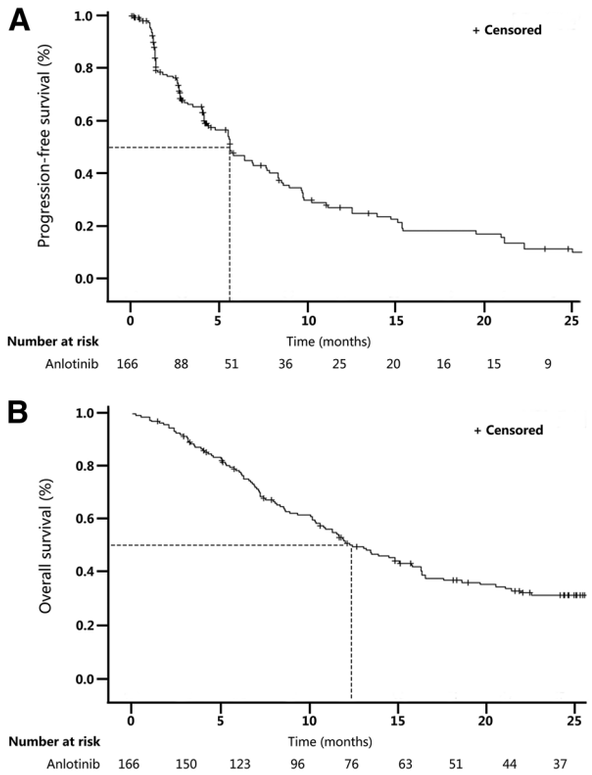

Figure 1.
Kaplan–Meier curves for PFS (**A**) and OS (**B**).

During the study, no complete responses were seen, but partial responses occurred in 21 patients: 1 with UPS; 1 with LPS; 2 with LMS; 8 with SS; 2 with FS; 6 with ASPS; and 1 with CCS. Overall in the FAS, the objective response rate was 13% (95% CI, 7.6–17; Fig. 2; Table 2), the disease control rate was 74% (95% CI, 66–80).

Toxicity

Table 3 summarizes the adverse events that happened in more than 10% of all patients. The most common grade 1/2 adverse events were triglyceride elevation (44%), hand–foot skin reaction (43%), hypertension (42%), fatigue (37%), proteinuria (37%), and pharyngalgia (32%). The most common grade 3/4 adverse events were hypertension (4.8%), triglyceride elevation (3.6%), and pneumothorax (2.4%). No treatment-related death occurred. Dose reductions occurred in 24 patients.

Discussion

The substantial heterogeneity of STS entities dramatically influenced the sensitivity to specific agents in different STS entities (26). For example, trabectedin is mainly active in LPS and LMS (8, 9), eribulin in LPS (10), and pazopanib in nonadipocytic sarcomas (11). The findings from this phase II trial showed that anlotinib has promising antitumor activity against metastatic STS after the failure of anthracycline-contained chemotherapy. In each cohort, the $PFR_{12\ weeks}$ exceeded 40%. Our study has covered almost all subtypes of STS, including SS, LMS, FS, UPS, LPS, ASPS, and CCS, which makes the results valuable for the majority of patients with metastatic STS.

Several eligible histologic types of STS showed a high sensitivity to anlotinib, such as FS, ASPS, LPS, and SS, with the $PFR_{12\ weeks}$ of all those subtypes exceeding 70%. Interestingly, patients with LPS seemed to gain more benefit from anlotinib when compared with other multi-kinase inhibitors, with a $PFR_{12\ weeks}$ of 63% in this study. As a contrast, in the phase II study of pazopanib in STS, the $PFR_{12\ weeks}$ was only 26% in adipocytic sarcoma cohort, leading to early close of recruitment in this subgroup (23). In the REGOSARC study, regorafenib also failed to improve PFS and PFR at 3 months compared with placebo in this specific subgroup (27). Although the subject number of LPS was relatively small ($n = 13$), anlotinib is the first multi-kinase inhibitor that showed a promising efficacy against LPS. A larger sample size for further verification is needed.

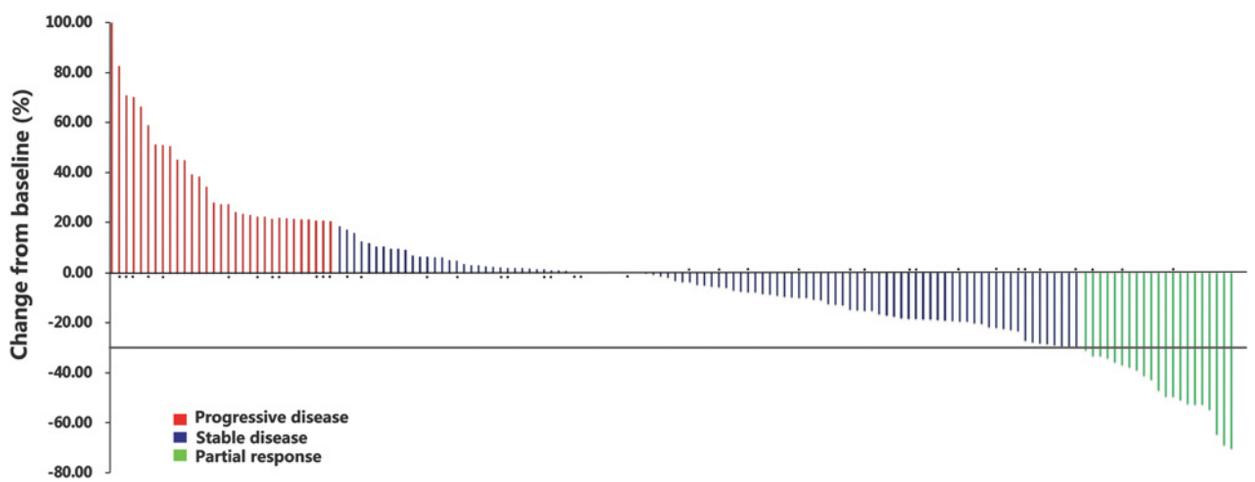

Figure 2.
Waterfall plot for best percentage change in target lesion size are shown. Maximum reduction from baseline (or smallest increase from baseline for patients with no reductions) in the sum of the longest diameters of target lesions. The change from baseline in tumor measurement as assessed by investigator review is shown for 154 patients (PPS). Gray line represents the threshold for partial response (>30% reduction from baseline sum of longest diameters). The target changes of patients from the initial 43 patients enrolled were marked with black squares. Target lesions were defined according to RECIST 1.1.

Table 2. Progression, survival, and efficacy data of each cohort and overall patients

	UPS	LPS	LMS	SS	FS	ASPS	CCS	Other sarcoma	Patients (initial 43)	Patients (subsequent 123)	Overall patients
Sample size	19	13	26	47	18	13	7	23	43	123	166
PFR (%)											
At 12 weeks	58	63	75	75	81	77	54	44	53	73	68
At 24 weeks	36	53	69	53	44	77	54	24	35	57	51
At 36 weeks	14	0	50	41	27	77	54	12	16	44	37
Median PFS (months)	4.1	5.6	11	7.7	5.6	21	11	2.8	5.3	6.2	5.6
Survival rate (%)											
At 6 months	62	92	84	82	78	100	57	60	67	82	78
At 12 months	28	50	55	49	44	100	57	46	35	57	51
At 24 months	11	42	36	23	22	92	19	24	23	35	32
Median OS (months)	11	13	15	12	12	NR	16	8.8	9.9	13	12
Objective response rate (%)	5.3	7.7	7.7	17	11	46	14	0.0	7	15	13

Abbreviation: NR, not reached.

In the present study, the median PFS of ASPS was 21 months, suggesting a significant benefit from anlotinib which was consistent with other antiangiogenic drugs in this population. Pazopanib, another multi-targeted tyrosine kinase inhibitor, prolonged the median PFS to 13.6 months (range, 1.6–32.2+ months; ref. 28). In a retrospective study of sunitinib, the median PFS of 9 advanced ASPS patients was 17 months (29). In the phase II trial conducted in 48 ASPS patients, cediranib demonstrated an improvement in PFS compared with placebo (10.8 vs. 3.7 months; ref. 30).

The median OS of patients with metastatic STS who failed the standard chemotherapy is approximately 6 to 10 months (12). Based on the phase III trial conducted in patients with nonadipocytic advanced STS, pazopanib demonstrated a significant improvement in PFS (4.6 vs. 1.6 months, HR 0.31; $P < 0.0001$) but not in OS (12.5 vs. 10.7 months, HR 0.86; $P = 0.25$) compared with placebo (11). Likewise, regorafenib improved PFS (4.0 vs. 1.0 months, HR 0.36; $P < 0.001$) but not OS (13.4 vs. 9.0 months, HR 0.67; $P = 0.059$) in REGOSARC study (27). In the present study, the median OS of 166 patients was 12 months, which was comparable with the survival data of pazopanib and regorafenib, suggesting a survival benefit might also be achieved from anlotinib treatment.

Table 3. Safety profile

	Patients by event grade		
	Total	G1 or G2	G3 or G4
Events	*N* (%)	*N* (%)	*N* (%)
Triglyceride elevation	73 (44)	67 (40)	6 (3.6)
HFS reaction	71 (43)	70 (42)	1 (0.6)
Hypertension	70 (42)	62 (37)	8 (4.8)
Fatigue	62 (37)	62 (37)	0 (0)
Proteinuria	61 (37)	60 (36)	1 (0.6)
Pharyngalgia	53 (32)	53 (32)	0 (0)
Diarrhea	45 (27)	44 (27)	1 (0.6)
TSH elevation	43 (26)	41 (25)	2 (1.2)
Cholesterol elevation	32 (19)	32 (19)	0 (0)
Hypothyroidism	32 (19)	32 (19)	0 (0)
Hoarse	28 (17)	28 (17)	0 (0)
Anorexia	28 (17)	28 (17)	0 (0)
ALT elevation	26 (16)	25 (15)	1 (0.6)
AST elevation	22 (13)	22 (13)	0 (0)
Stomachache	20 (12)	19 (12)	1 (0.6)
TBIL elevation	18 (11)	18 (11)	0 (0)
GGT elevation	17 (10)	16 (10)	1 (0.6)
LDL elevation	17 (10)	17 (10)	0 (0)
Hyperglycemia	17 (10)	17 (10)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HFS reaction, hand–foot skin reaction; LDL, low density lipoprotein; TBIL, total bilirubin; TSH, thyroid-stimulating hormone.

The toxicity profile was generally consistent with the prior experience of anlotinib in phase I study and the safety data of other multi-kinase inhibitors belonging to the same class (31). The most frequent adverse events were triglyceride elevation, hand–foot skin reaction, hypertension, and fatigue. Being gratified, most of them were mildly graded, and the lipid metabolism and thyroid dysfunction were reversible. Only a small proportion of subjects reported grades 3/4 events. Among those, 4 patients (2.4%) with grades 3 pneumothorax easily claimed our attention, whereas the prevalence of spontaneous pneumothorax in sarcoma is 1.9% (32). Similar incidence of pneumothorax was also reported with pazopanib and regorafenib in this population (11, 27). Direct invasion of tumor or extension of cavitary tumor lesions could be the most probable causes. Further, necrosis of peripherally located pulmonary or pleural lesions in response to effective treatment is also likely to be responsible, as opposed to direct toxicity of treatment.

The present study had some limitations. A small proportion of patients (4.2%) who were not eligible still received treatment and were included in the analysis, which might cause disturbance when interpreting the results. Moreover, the planned ancillary analysis of clinical and biological predictive or prognostic factors will be reported in the future. All patients enrolled in this study were from China, and the generalizability to other populations needs to be discussed.

In conclusion, anlotinib was proved to have broad-spectrum antitumor activity in patients with several metastatic STS entities who were refractory to previous anthracycline-based chemotherapy. The toxicity was manageable and acceptable. A double-blind, placebo-controlled, phase III trial of anlotinib in ASPS, SS, and LMS is ongoing (NCT03016819).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y. Chi, Z. Fang, P. Sun, J. Wang, J. Cai
Development of methodology: Y. Chi, Z. Fang, P. Sun, J. Wang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Chi, Z. Fang, X. Hong, Y. Yao, P. Sun, G. Wang, F. Du, Y. Sun, Q. Wu, G. Qu, S. Wang, J. Song, J. Yu, Y. Lu, X. Zhu, X. Niu, Z. He
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Chi, Z. Fang, Q. Wu, G. Qu, H. Yu

Writing, review, and/or revision of the manuscript: Y. Chi, Z. Fang, X. Hong, Y. Yao, G. Wang, F. Du, Y. Sun, Q. Wu, Y. Lu, Z. He, J. Wang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Fang, P. Sun, Y. Sun, G. Qu, X. Niu, H. Yu
Study supervision: Y. Chi, Z. Fang, X. Hong, Y. Yao, P. Sun, G. Wang, F. Du, Y. Sun, Q. Wu, Y. Lu, J. Wang

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