



Efficacy and safety of apatinib in advanced refractory soft tissue sarcoma and association with histologic subtypes: a multicenter retrospective study

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Background: Antiangiogenic therapy is a potential strategy against advanced refractory soft tissue sarcoma (STS). This retrospective study aimed to assess the efficacy and safety of apatinib in patients with advanced refractory STS and explore its clinical effect on the different histologic subtypes.

Methods: Patients with pathologically diagnosed and metastatic STS who had failed at least standard chemotherapy and were naive to angiogenesis inhibitors were enrolled in this multicenter retrospective study. Apatinib was administered orally at a dosage of 250 to 850 mg/day. The primary endpoints were objective response rate (ORR) and disease control rate (DCR). The secondary endpoints were progression free survival (PFS) and overall survival (OS). Tumor assessment was done after the first 4 weeks and every 8 weeks thereafter.

Results: Twenty-six patients were enrolled from seven centers between December 2015 and December 2020, consisting of 9 leiomyosarcomas (LMS), 4 rhabdomyosarcomas (RMS), 3 undifferentiated pleomorphic cell sarcomas (UPS), 3 fibrosarcomas (FS), 3 alveolar soft part sarcomas (ASPS), 2 angiosarcomas (AS) and 2 synovial sarcomas (SS). The median age was 49.0 [26–77] years, 15 females and 11 males. The ORR was 34.62% [9/26, 95% confidence interval (CI): 19.42–53.78%] and DCR was as high as 84.62% (22/26, 95% CI: 66.47–93.85%). The median progression-free survival and overall survival were 6.0 months (95% CI: 2.42–9.58) and 19.3 months (95% CI: 7.31–31.29) respectively. Furthermore, 181 patients from seven studies as well as this trial were included for pooled analysis of apatinib efficacy dependency on histology. In terms of ORR, RMS (41.7%), ASPS (78.6%), and Ewing sarcoma (40.7%) seemed to benefit more than the other histologic subtypes. Common adverse events (AEs) included hand-foot skin reaction (n=13, 50.0%), hypertension (n=12, 46.15%), proteinuria (n=10, 38.46%). Seven patients (7/26, 26.92%) had grade 3 AEs and no grade 4 AEs occurred. 2 patients (2/26, 7.69%) and 15 patients (15/26, 57.69%) experienced dose withdrawal and dose reduction respectively.

Conclusions: Apatinib showed promising efficacy and a manageable safety profile in patients with advanced refractory STS. In addition, the response to apatinib in STS seemed to be dependent on histology.

Keywords: Apatinib; advanced refractory soft tissue sarcoma; efficacy; safety

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Introduction

Soft tissue sarcoma (STS) is a rare and highly heterogeneous malignant tumor that can develop from any mesenchymal tissue of the whole body. Its histopathologic subtypes number more than 75 World Health Organization (WHO) Classification of Tumors: Soft Tissue and Bone Tumors, 2013) (1) with distinct genetic profiles and prognosis (2). For most patients with unresectable and metastatic STS, doxorubicin alone or in combination with ifosfamide or other cytotoxic agents has been the mainstay of palliative systemic therapy, regardless of histologic subtype (3,4). Before 2015, only a few new drugs were approved for use after failure of standard chemotherapy, including trabectedin for leiomyosarcoma (LMS) and liposarcoma, and pazopanib as an antiangiogenic tyrosine kinase inhibitor (TKI) for non-adipocytic and non-gastrointestinal stromal tumor (GIST) STS (5,6). Pazopanib significantly increased progression free survival (PFS) when compared with placebo (4.6 vs. 1.6 m) in 369 patients with advanced non-adipocytic soft-tissue sarcoma in the phase III Pazopanib for metastatic soft-tissue sarcoma (PALETTE) trial (6). Since the approval of pazopanib, many new antiangiogenic TKIs had entered clinical trials to evaluate their activity in STS as a second- and late-line treatment, including regorafenib and anlotinib (7). Both regorafenib and anlotinib significantly prolonged PFS with advanced soft tissue sarcoma, especially in some histological subtypes, such as alveolar soft part sarcomas (ASPS) (8-10).

Apatinib, as a highly selective vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor, was the first domestic antiangiogenic TKI approved in China in 2014 to treat advanced and refractory gastric cancer patients with promising survival benefit (11,12). In addition, apatinib has demonstrated substantial potential to treat a variety of tumor types (13). There were also several published reports documenting the promising efficacy of apatinib in soft tissue sarcomas, such as osteosarcoma, angiosarcoma (AS), undifferentiated pleomorphic sarcoma (UPS), ASPS and myxoid/round cell liposarcoma (13-18). Therefore, after its approval in China for gastric cancer, we conducted this retrospective study to evaluate the efficacy and safety of apatinib in the real world advanced refractory STS.

Furthermore, there is emerging evidence that treatment

for advanced sarcoma is being increasingly driven by histology (19). A precision medicine approach should take into account the sarcoma histologic subtype as well as the goals of care, performance status, and toxicity thresholds of individual patients. In PALETTE, STS patients were categorized based on tumor histology into three categories: synovial sarcomas (SS), LMS, and other subtypes (6). Adipocytic sarcoma was excluded based on the lack of response and survival benefit in the European Organisation for Research and Treatment of Cancer (EORTC) phase II trial (study 62043) (20). Pazopanib seemed to be more effective in synovial sarcomas and LMS, but the difference was not statistically significant. Therefore, it is of great interest to elucidate whether the efficacy of apatinib is associated with histology as a guide to individualized treatment. We present the following article in accordance with the TREND reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3250/rc>).

Methods

Study design and patients

We carried out a retrospective study to evaluate the efficacy and safety of apatinib for STS patients. From December 2015 to December 2020, 26 patients from seven centers (Department of Medical Oncology, Qilu Hospital of Shandong University, Jinan, China; Fifteenth Inpatient Area of Surgery, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China; Department of Proton Center, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China; Department of Oncology, Jining First People's Hospital, Jining, China; Department of Radiation Therapy, the Forth People's Hospital of Jinan, Jinan, China; Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China; Department of Oncology, The Fourth People Hospital of Zibo, Zibo, China) in China with advanced refractory and metastatic STS were enrolled. Eligible patients were required to (I) be ≥ 16 years old; (II) have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2; (III) have progression after standard chemotherapy; (IV) be antiangiogenic therapy-naïve; (V)

have life expectancy >3 months; and (VI) have at least one measurable lesion according to RECIST 1.1.

The main exclusion criteria were: (I) prior treatment with an antiangiogenic agent such as sunitinib, sorafenib, and bevacizumab; (II) known history of or concomitant malignancy; (III) chemotherapy or radiotherapy within 28 days before study entry; (IV) participation in another clinical trial within 28 days before study entry; (V) > grade 2 bleeding within 28 days according to Common Terminology Criteria for Adverse Events v 4.0 (CTCAE); (VI) abnormal international normalized ratio within 14 days; (VII) inability to swallow oral medications; and (VIII) any history of arterial or deep venous thrombus, or known history of brain or meningeal metastasis, and spinal compression. The sample size was calculated based on the data from PALETTE trial (6) and the following hypothesis. The PFS of BSC (best supportive care) as historical control and pazopanib as a reference was about 2 months and 4.6 months respectively in refractory soft tissue sarcomas. Supposing the estimated PFS of apatinib to be 4 months, at least 14 patients were needed to detect the targeted difference from BSC (2 months) with 90% power at a 5% significance level. We screened 55 patients and 29 of whom were excluded because of incomplete clinical data. Finally, 26 patients met the inclusion criteria and carried on the efficacy and safety analysis.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Qilu Hospital of Shandong University (No. 2015078). All participating centers were informed and agreed the study. Written informed consent was given by all patients, and for the patients under 18 years old, informed consent was also obtained from their legal guardians.

Treatment protocol

All subjects received apatinib orally at a starting dosage of 250 to 850 mg/day after meals, until disease progression, death, unacceptable toxicity. Subjects who could not tolerate the 250 mg dose were excluded from the trial.

Efficacy and safety evaluation

Pretreatment evaluation included physical examination, clinical blood counts and blood chemistry, and computed tomography scans of measurable lesions at baseline. During

the treatment period, tumor assessment and adverse events (AEs) evaluation were done after the first 4 weeks and every 8 weeks thereafter. All patients were followed up for survival (until death from any cause). The primary endpoints were the objective response rate (ORR) and disease control rate (DCR) (12 weeks). The secondary endpoints were PFS, overall survival (OS) and safety profiles. The end of last follow-up was 31 December 2020 and the median follow-up was 22.3 months.

Systematic review, study selection and data extraction

For the literature review, by searching PubMed, Embase, and the Cochrane Central Register of Controlled Trials, studies fulfilling the following criteria were included: (I) enrolled patients with histologically confirmed STS; (II) patients treated with oral apatinib at a daily dose of 250–850 mg; and (III) clinical efficacy outcomes reported by histology as tumor response, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The main exclusion criteria were: (I) no accessible response data by histology; and (II) participants received concomitant medication (e.g., chemotherapeutic agents) during the period of apatinib administration. 7 studies were enrolled after selection. The extracted information mainly included patient numbers for CR, PR, SD and PD. Responses of STS to apatinib at 12 weeks were pooled and compared between different histologic subtypes.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. Survival analysis was performed by Kaplan-Meier method. Fisher's exact test and chi-square test were used to compare the efficacy among different histologic subtypes. All statistical analyses were two-sided, and significance was set at $P < 0.05$.

Results

Patients' characteristics

The basic characteristics of the STS patients are listed in *Table 1*. A total of 26 patients with advanced refractory STS from seven centers between December 2015 to December 2020 were included, consisting of 9 leiomyosarcomas, 4 rhabdomyosarcomas, 3 undifferentiated pleomorphic cell sarcomas, 3 fibrosarcomas, 3 alveolar soft part sarcomas, 2

Table 1 Clinicopathological characteristics of patients with sarcoma treated with apatinib

Characteristics	Apatinib group (n=26)
Sex, n (%)	
Male	11 (42.31)
Female	15 (57.69)
Age (years), median [range]	49.0 [26–77]
ECOG performance score, n (%)	
0	9 (34.62)
1	14 (53.85)
2	3 (11.54)
Histologic subtype, n (%)	
Leiomyosarcoma	9 (34.62)
Rhabdomyosarcoma	4 (15.38)
Undifferentiated pleomorphic cell sarcoma	3 (11.54)
Fibrosarcoma	3 (11.54)
Alveolar soft part sarcoma	3 (11.54)
Angiosarcoma	2 (7.69)
Synovial sarcoma	2 (7.69)
Resection of primary lesion, n (%)	
Yes	25 (96.15)
No	1 (3.85)
Metastatic site, n (%)	
Lung	14 (53.85)
Other	12 (46.15)
Line of previous chemotherapy, n (%)	
1	0 (0.0)
2	18 (69.23)
3	8 (30.77)

ECOG, Eastern Cooperative Oncology Group.

angiosarcomas and 2 synovial sarcomas. The median age was 49.0 [26–77] years, and there were 15 females and 11 males. Most patients (96.15%) underwent resection of the primary lesions. All patients had ≥ 1 distant metastasis and the lungs (53.85%) were the most involved organ. A total of 18 cases (69.23%) of failed second-line chemotherapy and 8 (30.77%) of failed third-line chemotherapy or more.

Efficacy

At 12 weeks, all 26 patients had received at least one treatment cycle and were included in our efficacy evaluation (Figure 1). None achieved CR, 9 achieved PR (34.62%), 13 achieved SD (50.0%), and 4 patients had PD (15.38%). The ORR at 12 weeks was 34.62% [9/26, 95% confidence interval (CI): 19.42–53.78%], the DCR was 84.62% (22/26, 95% CI: 66.47–93.85%). At the end of follow-up, 1 patient was still free from progression and 9 were still alive. The median PFS was 6.0 months (95% CI: 2.42–9.58) (Figure 2A) and the median OS was 19.3 months (95% CI: 7.31–31.29) (Figure 2B).

Correlation of histologic subtypes with response to apatinib and the systematic review

As shown in Table 2, 7 studies (14,21–27) as well as this trial with 181 participants were included for analysis of efficacy dependency on histology. Two patients with hemangiopericytoma and malignant granulosa cell tumor were excluded. The ORR and DCR in the unspecified patients were 32.4% (58/179) and 77.7% (139/179) respectively. Regarding the different STS types, there were varying response rates of apatinib among them. Rhabdomyosarcomas, undifferentiated pleomorphic cell sarcomas, alveolar soft part sarcomas and Ewing sarcoma were more sensitive to apatinib, while synovial sarcoma, angiosarcoma, leiomyosarcomas, malignant peripheral nerve sheath tumor, liposarcoma, clear cell sarcoma and epithelioid sarcoma responded much less to apatinib (Figure 3).

Safety

Common AEs included hand-foot skin reaction (HFS) (n=13, 50.00%), hypertension (n=12, 46.15%), proteinuria (n=10, 38.46%), nausea (n=5, 19.23%), fatigue (n=4, 15.38%), and abdominal pain (n=4, 15.38%). No grade 4 AEs occurred, but 7 patients (7/26, 26.92%) had grade 3 AEs, mainly hypertension, fecal occult blood and HFS (Table 3). Two (7.69%) patients quit the trial during treatment because of grade 3 HFS and fecal occult blood respectively. The proportion of dose reduction caused by the different grades of AEs was 57.69% (15/26), 2 patients (n=2, 7.69%) experienced dose withdrawal.

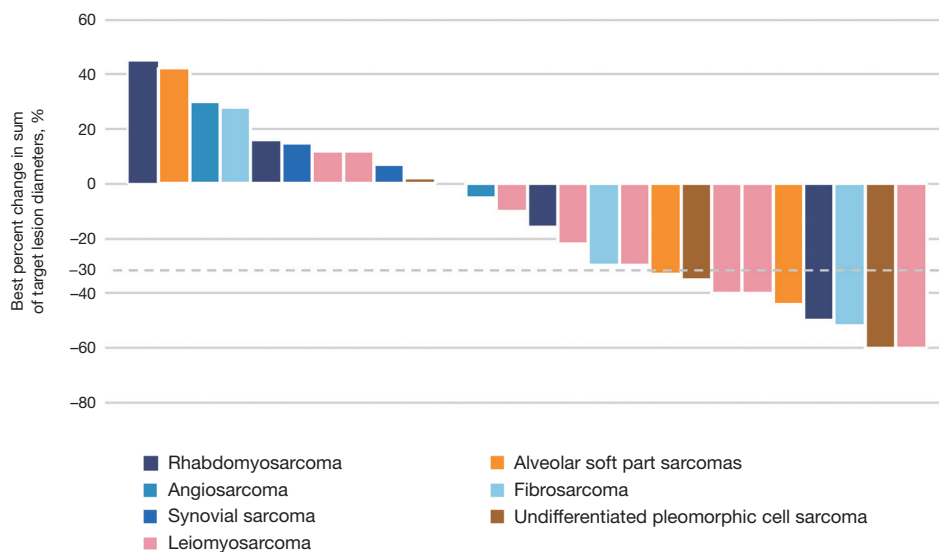


Figure 1 Maximum changes in the target lesions in patients with advanced and refractory sarcomas treated with apatinib. Dotted line represents the threshold for partial response (>30% reduction from baseline sum of longest diameters). Target lesions were defined according to RECIST 1.1.

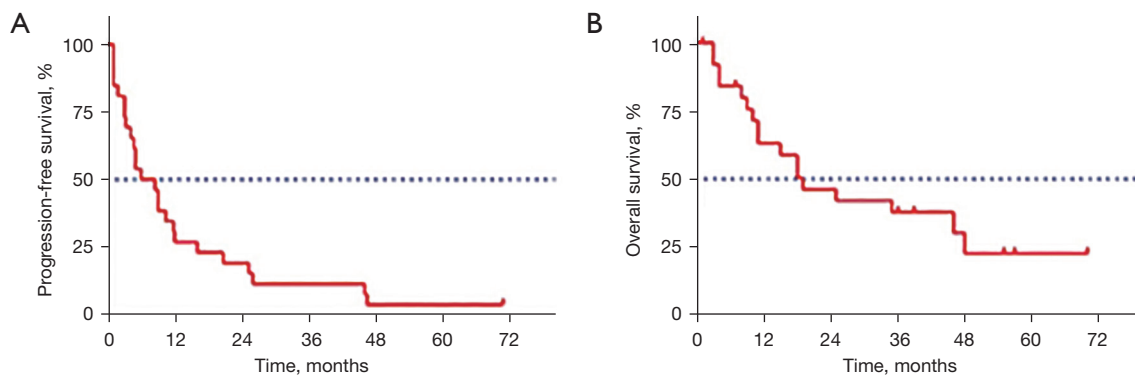


Figure 2 Kaplan-Meier survival curves of progression-free survival (A) and overall survival (B) of advanced and refractory soft tissue sarcoma.

Discussion

Although there have been significant advances in the understanding of pathogenesis and progression of STS, the prognosis of advanced refractory STS patients remains dismal. So far, no standard therapy has been established beyond first-line treatment. Overexpression of angiogenic factors such as VEGF and VEGFR has been reported to be significantly associated with low survival in patients with sarcoma (28,29). Because angiogenesis is an essential

prerequisite of growth and dissemination of STS, blockade of VEGF/VEGFR pathways becomes a promising therapeutic strategy.

As a new and highly selective TKI against VEGFR-2, apatinib was shown in our study to be effective for treating advanced refractory STS, based on the ORR (34.62%), and DCR (84.62%) at 12 weeks, median PFS (6.0 months), and median OS (19.3 months), which was in accord with two previous prospective studies (22,30). In a recent systematic

Table 2 Response of different histologic subtypes to apatinib at 12 weeks in the present and other studies

STS subtype	Xie L (n=18*) (21)			Liu and Liao (n=45) (22,23)			Tian Z (n=49) (24)			Wang Y (n=37) (25-27)			Li F (n=6) (14)			The present study (n=26)			Total (n=181*, %)							
	CR+ PR	SD	PD	CR+ PR	SD	PD	CR+ PR	SD	PD	CR+ PR	SD	PD	CR+ PR	SD	PD	CR+ PR	SD	PD	CR+ PR	SD	PD	DCR				
LMS	0	3	2	0	3	2	1	2	3	0	0	1	0	0	1	3	6	0	4	11	52.4	6	28.6	15	71.4	
RMS	4	1	0	4	1	0	0	2	1	0	0	0	0	0	0	1	2	1	5	41.7	5	41.7	2	16.7	10	83.3
UPS	2	4	0	2	4	0	4	4	2	0	0	1	0	0	1	2	1	0	8	40.0	9	45.0	3	15.0	17	85.0
FS	1	0	0	1	3	1	0	1	1	0	2	0	0	2	0	1	1	1	3	23.1	7	53.8	3	23.1	10	76.9
ASPS	2**	0	1**	0	1	0	1	0	0	6	0	0	0	0	0	2	0	1	11	78.6	1	7.1	2	14.3	12	85.7
AS	1	0	0	1	0	0	1	2	1	0	0	1	0	1	0	0	1	1	2	28.6	3	42.9	2	28.6	5	71.4
SS	1	4	0	1	4	0	1	4	2	9	8	4	0	2	0	0	2	0	11	29.7	20	54.1	6	16.2	31	83.8
MPNST	2	1	0	1	4	1	0	1	3	0	0	1	0	1	0	0	0	0	3	23.1	6	46.2	4	30.8	9	69.2
LS	0	0	1	0	1	1	0	3	2	0	0	1	0	3	2	0	0	0	0	0.0	4	50.0	4	50.0	4	50.0
EWS	7***	1	2	0	7	0	0	0	0	4	4	2	0	0	0	0	0	0	11	40.7	12	44.4	4	14.8	23	85.2
CCS	0	1	0	0	1	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0.0	2	50.0	2	50.0	2	50.0
ES	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	1	33.3	2	66.6	1	33.3
STS																			58	32.4	81	45.2	40	22.3	139	77.7

*, only patients with histologic subtype and clinical efficacy outcomes are included; **, 3 cases of ASPS were treated with apatinib combined with chemotherapy, there was consensus among experts that ASPS is not effective for chemotherapy, clinical efficacy was the role of apatinib, and therefore included; ***, 10 cases of EWS, partially treated with apatinib combination, with indistinguishable efficacy evaluation, were included. AS, angiosarcoma; ASPS, alveolar soft part sarcoma; CCS, clear cell sarcoma; CR, complete response; ES, epithelioid sarcoma; EWS, Ewing sarcoma; FS, fibrosarcoma; LMS, leiomyosarcoma; LS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; PR, partial response; RMS, rhabdomyosarcoma; SD, stable disease; SS, synovial sarcoma; PD, progressive disease; STS, soft tissue sarcoma; UPS, undifferentiated pleomorphic sarcoma; DCR, disease control rate.

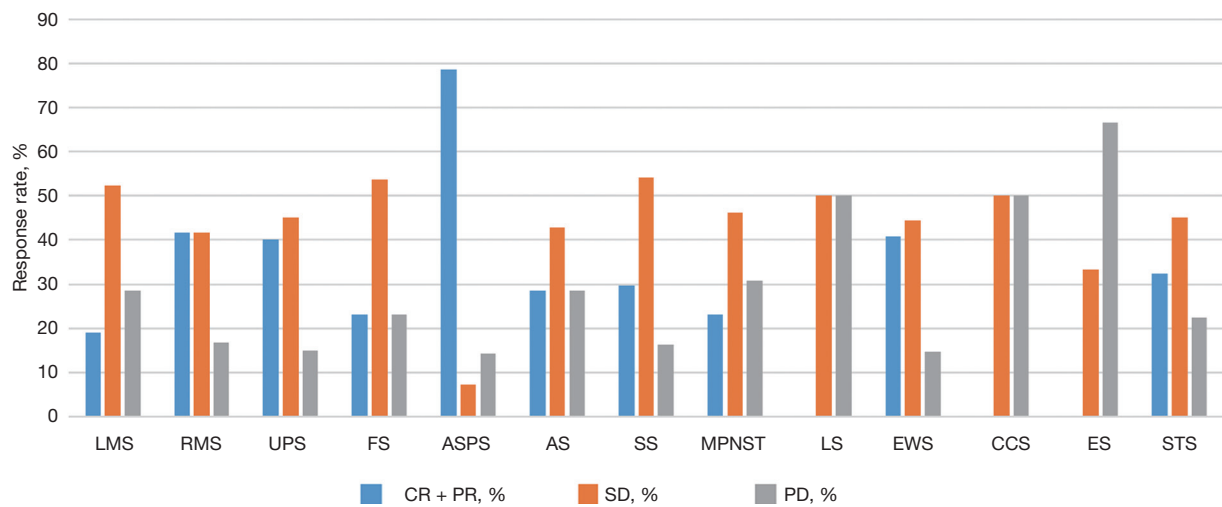


Figure 3 Response of different soft tissue sarcoma types to apatinib at 12 weeks. AS, angiosarcoma; ASPS, alveolar soft part sarcomas; CCS, clear cell sarcoma; CR, complete response; ES, epithelioid sarcoma; EWS, Ewing sarcoma; FS, fibrosarcoma; LMS, leiomyosarcoma; LS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; PR, partial response; PD, progression disease; RMS, rhabdomyosarcoma; SD, stable disease; SS, synovial sarcoma; STS, soft tissue sarcoma; UPS, undifferentiated pleomorphic sarcoma.

Table 3 Adverse events in STS patients treated with apatinib

Adverse event	Patients by event grade		
	Total, n (%)	1 or 2, n (%)	3 or 4, n (%)
Hand-foot skin reaction	13 (50.00)	9 (34.62)	4 (15.38)
Proteinuria	10 (38.46)	10 (38.46)	0 (0)
Hypertension	12 (46.15)	10 (38.46)	2 (7.69)
Nausea	5 (19.23)	5 (19.23)	0 (0)
Fatigue	4 (15.38)	4 (15.38)	0 (0)
Abdominal pain	4 (15.38)	4 (15.38)	0 (0)
Diarrhea	2 (7.69)	2 (7.69)	0 (0)
Fecal occult blood	1 (3.85)	1 (3.85)	0 (0)
Leucopenia	1 (3.85)	1 (3.85)	0 (0)
Thrombocytopenia	1 (3.85)	1 (3.85)	0 (0)
Urine occult blood	2 (7.69)	2 (7.69)	0 (0)
Hair hypopigmentation	1 (3.85)	1 (3.85)	0 (0)
Fecal occult blood	2 (7.69)	1 (3.85)	1 (3.85)
Liver dysfunction	2 (7.69)	2 (7.69)	0 (0)
Vomiting	1 (3.85)	1 (3.85)	0 (0)

STS, soft tissue sarcoma.

review, 239 unspecified STS patients treated with apatinib were included for combined analysis, and both the ORR (29.03%) and DCR (79.94%) were similar to our results (31). Although only 26 STS patients were recruited, we believe our study provides valuable and promising additional information on the antiangiogenic strategy for advanced STS after failure of conventional chemotherapy.

With regard to the efficacy of different TKIs in a Chinese STS cohort, although both anlotinib and apatinib have been widely used in China, only a few studies have retrospectively compared the two drugs (24). Anlotinib was approved by the Chinese NMPA in June 2019 based on a phase IIB trial in refractory metastatic STS. A total of 166 patients were included and treated with anlotinib, but notably several entities were excluded, such as rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing sarcoma, primitive neuroectodermal tumor, inflammatory myofibroblastic tumor, etc. The PFS rate at 12 weeks was 68%, and ORR was 13%. The median PFS and median OS were 5.6 and 12 months respectively (8). Tian *et al.* retrospectively compared the efficacy of anlotinib and apatinib in advanced STS patients who failed after first-line chemotherapy at least. The basic clinical characteristics of the STS patients treated with apatinib (n=49) and anlotinib (n=29) were comparable, and no difference was observed in the ORR (12.24% *vs.* 13.79%), DCR (59.18% *vs.* 55.17%), and median PFS (7.82 *vs.* 6.03 months) (24). Moreover, pazopanib, though not approved in China, has proved to be effective in Japanese and Taiwanese STS patients (32,33).

Regarding the different STS types in the systematic review, apatinib was shown to be more active against most STS subtypes, such as rhabdomyosarcomas, undifferentiated pleomorphic cell sarcomas, alveolar soft part sarcomas, Ewing sarcoma, but synovial sarcoma and angiosarcoma, leiomyosarcomas, malignant peripheral nerve sheath tumor, liposarcoma, clear cell sarcoma and epithelioid sarcoma responded much less to apatinib. According to Fisher's exact test in the previous two studies, no significant difference was seen in response to apatinib by histologic subtype (22,30). The reason for the discrepancy mainly resulted from the small numbers in each study. In addition, the combination of different STS histologic proportions, especially those with different sensitivity to apatinib, might contribute to the wide variation in the response rate (95% CI: 20.53–41.06%) in the meta-analysis (31). For example, the response rate as high as 32.4% to apatinib in the combined 179 cases in our review might have resulted from having more of the responsive STS subtypes and also

indicated the broad-spectrum antitumor activity of apatinib. Likewise, the efficacy of both pazopanib and anlotinib is driven by histology (8,20). Pazopanib was less active in adipocytic sarcoma in the EORTC Study 62043. In one Japanese Musculoskeletal Oncology Group (JMOG) study, which collected real-life, postmarketing surveillance data, liposarcoma gained the least benefit from pazopanib. The rate of PR and the median OS for liposarcoma ranked the lowest at 0% and 7.3 months respectively (33). However, with regard to anlotinib, it showed a promising efficacy against liposarcoma, with ORR 7.7% and median OS 13 months. Unfortunately, only a few liposarcoma patients were included in the studies of apatinib, rendering it difficult to draw a conclusion (8). Alveolar soft part sarcoma was the most sensitive STS to pazopanib, anlotinib and apatinib, with ORR 33.3% and 46% and 73.3% respectively (8,33).

Regarding safety, apatinib was well tolerated in our study. The most frequently observed AEs associated with apatinib were hypertension, HFS, proteinuria, nausea and fatigue, in line with the findings of a phase III study of apatinib in chemotherapy-refractory advanced or metastatic gastric cancer (12). Treatment-related grade 3 AEs were HFS (15.38%) and hypertension (7.69%). There were no treatment-related deaths. Although all patients in this study had different degrees of AE, most of them were grade 1 and grade 2, which could be well controlled by reducing the dose or interrupting and/or symptomatic treatment, so as to be predictable, controllable and reversible.

The present study had some limitations. First, although the encouraging and remarkable efficacy of apatinib in this study was a valuable supplement to the antiangiogenic strategy in advanced STS after failure of conventional chemotherapy, this is a retrospective study with comparatively small number of 26 STS patients and high heterogeneity of 7 histologic subtypes warrant further cohort expansion and the generalizability to other populations needs to be explored. Second, in the systematic review and combined analysis of efficacy correlation with subtype, only the response rate and disease control rate driven by histology were used as endpoints; PFS and OS by histology were not available in most studies. Third, whether liposarcoma gained survival benefit from apatinib remains to be determined in future research.

In conclusion, apatinib shows promising antitumor activity in STS patients who are refractory to previous chemotherapy. The toxicity was manageable and acceptable. Because several histology entities exhibited remarkable

response to apatinib, such as alveolar soft part sarcoma, rhabdomyosarcomas, undifferentiated pleomorphic cell sarcoma and Ewing's sarcoma, earlier use in the first-line setting or in combination with conventional chemotherapy needs to be explored in future trials.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3250/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3250/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3250/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Qilu Hospital of Shandong University (No. 2015078). All participating centers were informed and agreed the study. Written informed consent was given by all patients, and for the patients under 18 years old, informed consent was also obtained from their legal guardians

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