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ORIGINAL RESEARCH

The Efficacy and Safety of Apatinib in Advanced Synovial Sarcoma: A Case Series of Twenty-One Patients in One Single Institution

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Background: Synovial sarcoma (SS) is a highly aggressive soft-tissue sarcoma (STS) with poor prognosis. Tyrosine kinase inhibitor (TKI) has shown a promising impact on advanced STS patients. This study aimed to evaluate the efficacy and safety of apatinib, an oral multi-TKI, which especially inhibited vascular endothelial growth factor receptor, as second-line therapy for patients with advanced SS.

Patients and Methods: This retrospective analysis included 21 advanced SS patients, who had a poor response to anthracycline-based chemotherapy alone or combined with ifosfamide at least one cycle. All the patients received an apatinib containing regimen between May 2016 and October 2019 in our institution. Apatinib 500–750 mg (250 mg for patients younger than 10) was given daily. Tumor responses were assessed by response evaluation criteria in solid tumors. Survival analysis was performed by the Kaplan–Meier test, and a safety profile was recorded.

Results: The median follow-up was 15.2 months (95% CI, 12.2-NE). Nine (42.9%) patients had partial response (PR), and eight (38.1%) had stable disease. The median progression-free survival (PFS) was 13.1 months (95% CI, 6.7-NE). The 6- and 12-month PFS rates were 76.2% (95% CI, 60.0–96.8) and 55.4% (95% CI, 37.3–82.3), respectively. Additionally, the median overall survival (OS) was 15.5 months (95% CI, 10.7-NE). The 6- and 12-month OS rates were 81.0% (95% CI, 65.8, 99.6) and 64.9% (95% CI, 46.9–90.0), respectively. Moreover, the objective response rate was 42.9% (9/21) for advanced SS patients. The disease control rate was 81.0% (17/21). For the nine patients with the best response of PR, the median duration of response was 7.7 months.

Conclusion: Apatinib was proved to be a potential second-line treatment option for advanced SS patients with chemo-resistance. Apatinib showed promising efficacy and acceptable safety profile in advanced SS, with considerable OS and particularly PFS. Indeed, further multicenter studies with a longer follow-up time are needed to fully determine the clinical application of apatinib in advanced SS.

Keywords: synovial sarcoma, apatinib, targeted therapy, efficacy, safety

Introduction

Synovial sarcoma (SS) is an aggressive malignancy of mesenchymal origin, accounting for approximately 8% to 10% of all soft-tissue sarcomas (STS).[1–3] SS is marked by the presence of a pathognomonic translocation between chromosomes X and 18, t(X;18)(p11.2;q11.2),[4] and its histological characteristics can be identified including monophasic, biphasic, and poorly differentiated SS.[4] Although SS frequently arises in the extremities, its histological feature is not related to synovial

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tissue.[5] As the common non-rhabdomyosarcoma STS in children and young adults, the peak incidence of SS is adolescents and adults younger than 30 years[5,7] Notably, SS has a high metastatic potential (approximately 24% of the patients at diagnosis) and a high locally recurrent rate (approximately 17% of patients).[8,9]

In general, SS is a high-grade sarcoma with a poor prognosis.[10] For local SS, the standard treatment was wide resection followed by radiation therapy in patients with high-risk disease (ie, deeply located tumor site, and tumor size>5 cm).[11] For advanced SS, anthracycline-based chemotherapy alone or combined with ifosfamide was regarded as the conventional frontline strategy.[12,13] However, controversy has still existed related to the most effective therapy regimen.[2] Once disease progression or chemo-resistance happened, no appropriate systemic agent is targeting the histologic or genomic characteristics of SS. Therefore, recently, several clinical trials on different approved palliative options have been reported, such as trabectedin,[14] pazopanib,[15] and regorafenib.[3]

Angiogenesis and multikinase inhibitors were recognized as active agents for advanced non-adipocytic sarcomas.[15,16] Although pazopanib and regorafenib were reported to significantly improve progression-free survival (PFS) compared with placebo in advanced SS patients, these treatment strategies did not improve the overall survival (OS).[3,16,17] Therefore, alternative options are needed. Apatinib is an oral anti-angiogenesis tyrosine kinase inhibitor (TKI) highly and selectively inhibitor on vascular endothelial growth factor receptor (VEGFR)-2.[18] Promising efficacy of apatinib was reported in advanced gastric cancer[19] and metastatic STS.[20]

No prior case series have described the efficacy and safety of apatinib in advanced SS. We further retrospectively studied the clinical outcomes of apatinib in 21 patients with advanced SS who have been previously treated at the Department of Orthopaedics of the West China Hospital.

Patients and Methods

Patients Eligibility

We examined advanced SS patients who were treated between May 2016 and October 2019 in our institution. The inclusion criteria were as follows: 1) histologically confirmed diagnosis of advanced SS according to the World Health Organization Classification of Tumours; 2) availability of complete data at the time of treatment including at least three measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; 3) intolerance or failure to anthracycline-based chemotherapy alone or combine with ifosfamide at least one cycle. This study was performed according to the principles embodied in the Declaration of Helsinki and the Institutional Review Board of Sichuan University West China Hospital. Written informed consent was obtained from all patients when they began treatment for apatinib. The study protocol followed all appropriate guidelines according to the Declaration of Helsinki.

Treatment Methods

Apatinib was orally administered at a dose of 750 mg for adults and 250 mg for children (less than 10 years of age) once a day for a 28-day cycle. In each cycle, one dose reduction (500–250 mg) was allowed for drug-related grade 3/4 adverse events (AEs). Treatment continued until disease progression or occurrence of unacceptable toxicities (grade 3/4 AEs) or patient refuel. Post-protocol treatment was discreetly managed by the patients and their physicians. The tumor response evaluation was based on computed tomographic or magnetic resonance imaging findings was performed every 2 months. Responses were assessed according to the RECIST 1.1.[21]

Statistical Analysis

Standard descriptive and analytic methods were used to describe the patient population and their baseline characteristics. Overall survival (OS) was defined as the time from the initiation of apatinib treatment to the date of death or last follow-up. Progression-free-survival (PFS) was defined as the time from initiation of the apatinib treatment to the date of documented disease progression or death from any cause. And OS and PFS were calculated using the Kaplan–Meier product-limit method. Disease control rate (DCR) was defined as the percentage of patients achieving a complete response (CR), partial response (PR) and stable disease (SD); objective response rate (ORR) was defined as the percentage of patients showing CR and PR. Duration of response (DOR) was defined as the length of time that the tumor continues to respond to treatment without progressive disease (PD). In addition, the 95% confidence interval (CI)s of the DCR, ORR, and DOR were calculated using an asymptotic normal approximation. A two-tailed $p < 0.05$ was considered statistically significant. The statistical analysis was

performed using SPSS version 23 software (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

Overall, 21 patients with metastatic or recurrent SS were treated with apatinib as at least a second-line chemotherapy. The baseline characteristic of the patients is summarized (Table 1). 47.6% (10) of the patients were male, and the median age was 31.5 ±14.0 years (range 8–71). The most common primary tumor sites were extremities (81.0%). All patients had undergone at least one first-line chemotherapy including: anthracycline-based agent alone (n=11, 52.4%) and anthracycline combined with ifosfamide (n=10, 47.6%). After first-line chemotherapy, 16 patients had distant metastasis, and 5 patients got local recurrence.

Table 1 Patient Characteristics

Total	Number of Patients (n)	Percentage (%)
Sex		
Male	10	47.6
Female	11	52.4
Age(years)		
Median	26.00	–
Range	8–71	–
Patients' status at the administration of apatinib		
Local recurrence	5	23.8
Metastasis	15	71.4
Both	1	4.8
Metastatic site		
Lung	14	66.7
Bone	2	9.5
Number of previous chemotherapy regimens chemotherapies		
1	5	23.8
2	11	52.4
≥3	5	23.8
ECOG PS		
0	1	4.8
1	13	61.9
2	5	23.8
3	2	9.5
Primary tumor site		
Extremities	17	81.0
Trunk	4	19.0

Efficacy

Among the 21 evaluable cases (Table 2), none of the patients were lost to follow-up and four patients died of lung metastasis. The median follow-up was 15.2 months (95% CI, 12.2-NE). Nine (42.9%) of 21 patients had PR, and eight (38.1%) had SD. We did notice dramatic tumor shrinkage (Figure 1). The median PFS was 13.1 months (95% CI, 6.7-NE) (Figure 2). The 6- and 12-month PFS rates were 76.2% (95% CI, 60.0–96.8) and 55.4% (95% CI, 37.3–82.3), respectively. Additionally, the median OS was 15.5 months (95% CI, 10.7-NE) (Figure 3). The 6- and 12-month OS rates were 81.0% (95% CI, 65.8, 99.6) and 64.9% (95% CI, 46.9–90.0), respectively. Moreover, the ORR was 42.9% (9/21) for advanced SS patients. The DCR was 81.0% (17/21). For the nine patients with the best response of PR, the median DOR was 7.7 months.

Safety and Toxicity

The common grade ≥1 non-hematological toxicities were hand-foot skin reaction (n = 7, 33.3%) and oral ulcers (n = 7, 33.3%) and vomiting (n = 6, 28.6%). The only grade 4 reaction was pneumothorax treated by dose reduction. And one patient discontinued apatinib because of hand-foot skin reaction. Most adverse reactions were mild (grades 1/2) and easily controlled (Table 3). And all the AEs were causally related to apatinib. No deaths were related to the experimental treatment.

Discussion

Although SS is a relatively chemo-sensitive STS compared with adipocytic STS,[12] the efficacy of neoadjuvant chemotherapy in advanced SS remains controversial.[22] Various targeted regiments are used as second-line treatments after the failure of anthracycline-based chemotherapy, such as sorafenib,[23] pazopanib,[15,16,24-27] regorafenib[3,17,28,29] and apatinib[20,30] (Table 4).

Among them, multitargeted TKIs can be effective in patients with metastatic or recurrent SS, which have different affinities against VEGFR −1/2/3, platelet-derived growth factor -α/β, fibroblast growth factor receptor (FGFR) −1/3, stem cell factor (c-Kit) receptor, and implicated in oncogenesis (TIE2, RET, RAF).[15,32] In previous studies, pazopanib and regorafenib had demonstrated acceptable antitumor activity with longer median PFS in metastatic or recurrent SS patients, compared with that of

Table 2 Clinical Characteristics of 21 Patients with Advanced SS Treated with Apatinib

Patients	Gender	Age	ECOG PS	Primary Site	Metastasis/ Recurrence	Surgery Before Apatinib	Initial Does(mg)	Overall Survival (m)	Progression Free Survival(m)	Medication Time(m)	Duration of Response(m)	Best Response
1	Male	21	1	Right hand	No/Yes	Yes	500	18.6	NA	18.6	NA	PR
2	Female	48	1	Left foot	Lung/No	Yes	500	13.8	NA	13.8	NA	PR
3	Male	24	1	Left thigh	Lung/No	Yes	500	14.8	8.7	8.7	8.7	PR
4	Female	36	1	Left pelvis	Lung/No	Yes	500	22.1	22.1	22.1	NA	SD
5	Female	8	1	Right foot	Lung/No	Yes	250	14.9	14.9	14.9	14.93	PR
6	Female	35	1	Right thigh	Lung/No	Yes	500	15.6	15.2	15.2	NA	SD
7	Male	31	1	Right calf	Lung/No	Yes	500	16.5	13.1	13.2	13.1	PR
8	Male	23	1	Right popliteal fossa	Lung/No	Yes	500	12.3	NA	12.3	NA	PR
9	Male	71	2	Left foot	Lung+bone/Yes	Yes	500	8.9	4.1	4.1	NA	PD
10	Female	46	3	Left hip	Lung+bone/No	Yes	500	2.8	1.6	2.8	NA	PD
11	Female	27	2	Right popliteal fossa	Lung/No	Yes	500	10.9	2.9	2.9	NA	SD
12	Male	25	1	Left forearm	Lung/No	Yes	500	10.9	6.4	7.9	6.4	PR
13	Female	21	2	Right thigh	Lung/No	Yes	500	10.8	6.7	6.8	6.7	PR
14	Male	28	0	Left thigh	No/Yes	Yes	500	10.7	NA	3.0	NA	SD
15	Female	26	1	Left thigh	Lung/No	Yes	500	10.0	NA	10.0	NA	PR
16	Female	23	1	Right hip	No/Yes	Yes	500	9.2	NA	9.2	NA	SD
17	Female	49	2	Right hip	Lung/No	Yes	500	3.1	NA	2.9	NA	PD
18	Female	26	1	Left thigh	Lung/No	Yes	500	5.9	NA	5.9	NA	SD
19	Male	21	1	Right elbow	No/Yes	Yes	500	12.2	NA	12.2	NA	SD
20	Male	48	2	Right popliteal fossa	Lung/No	Yes	500	3.9	1.8	1.8	NA	PD
21	Male	25	1	Right elbow	No/Yes	Yes	500	18.8	NA	18.8	NA	SD

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NA, not achieved

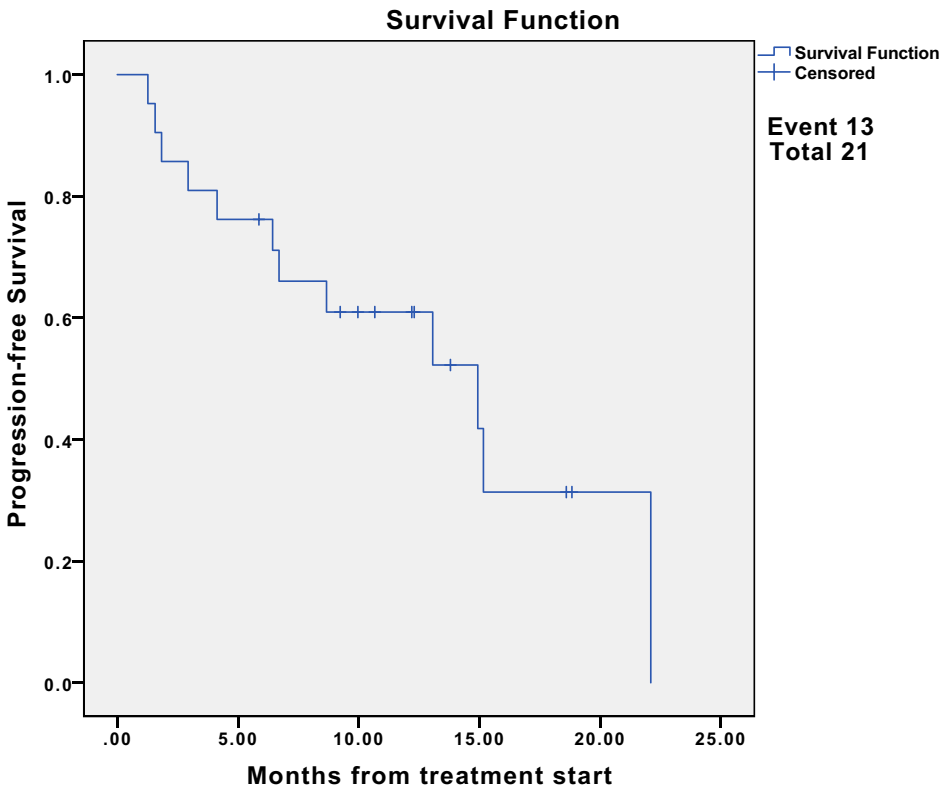


Figure 1 Maximum response to apatinib treatment.

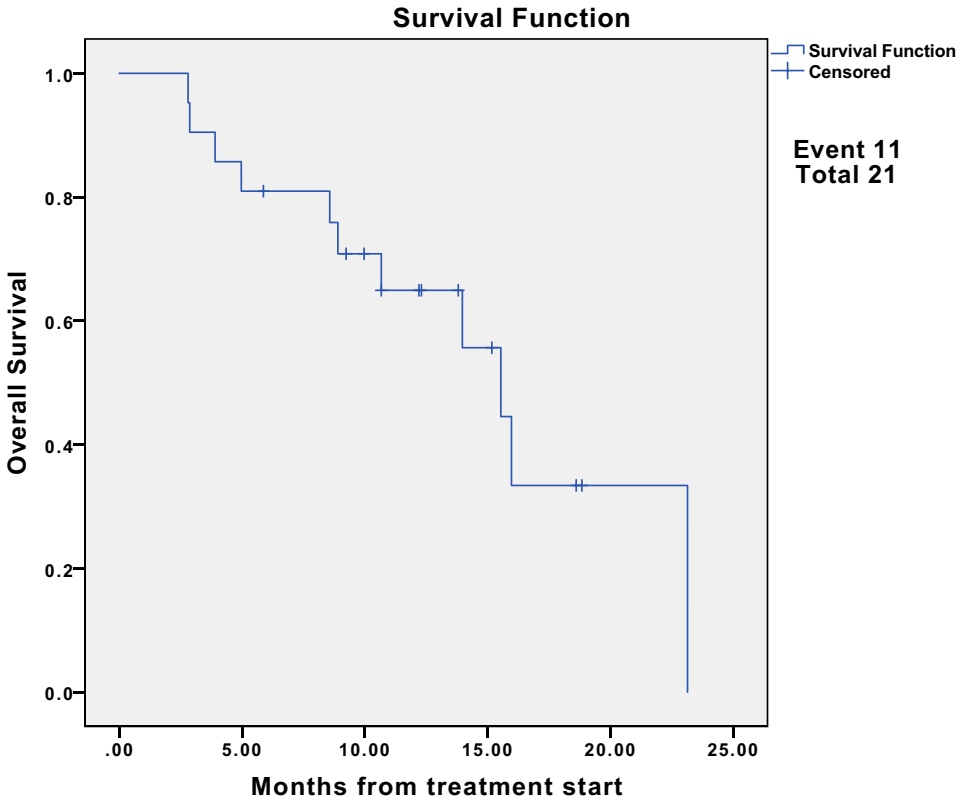


Figure 2 Kaplan–Meier estimates of progression-free survival for all patients.

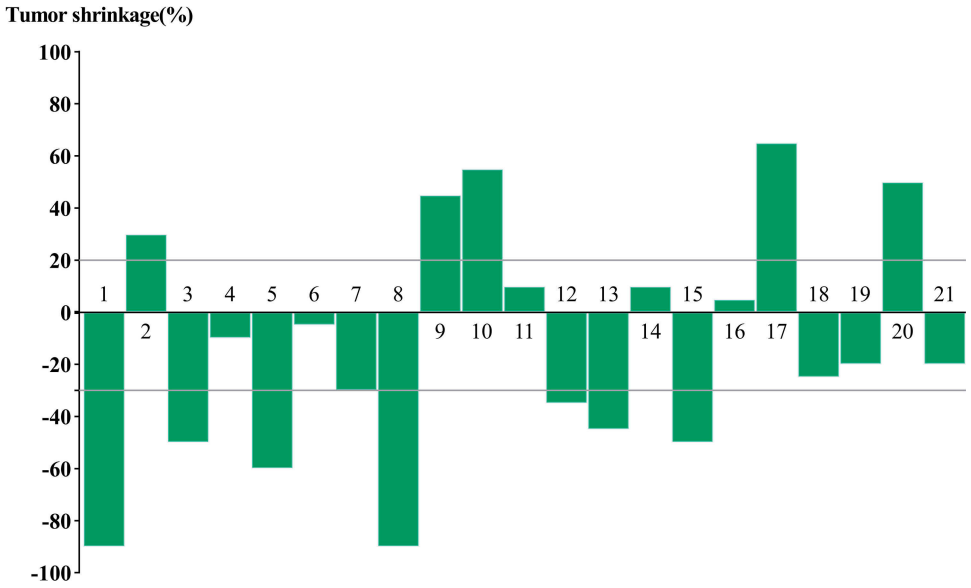


Figure 3 Kaplan–Meier estimates of overall survival for all patients.

the patients treated by placebo. However, pazopanib and regorafenib did not improve the median OS in the trials.[15,17] And, these drugs were not accessible to the Chinese investigators before January 2019.

Angiogenesis plays a crucial role in tumor growth, invasion, and development of metastasis.[33] Apatinib is an orally small-molecule VEGFR-TKI, which specifically and strongly inhibits VEGFR-2, decreasing VEGF-mediated endothelial cell migration, proliferation, and tumor microvascular formation.[19] In preclinical experiments, apatinib also impaired VEGF-stimulated proliferation, migration and tube formation by human umbilical vein endothelial cells, and blocked rat aortic ring budding in vitro, which may be associated with suppression of VEGFR-2-mediated phosphorylation of Ret, c-Kit, and c-src.[34] And apatinib has shown its anti-cancer effects in a variety type of tumors,[19] including STS.[20,30,31]

Table 3 Adverse Events

	Total N (%)	Grade		
AE		1	2	3–4
Hand-foot skin reaction	7	5	2	0
Oral ulcers	7	3	4	0
Vomiting	6	3	3	0
Anorexia	5	3	2	0
Hair hypopigmentation	4	2	2	0
Abdominal distention	4	2	2	0
Elevated Aminotransferase	2	1	1	0
Diarrhea	2	1	1	0
Headache	2	2	0	0
Pneumothorax	2	0	1	1
Menstrual Irregularities	2	1	1	0
Fatigue	1	0	1	0
Wound-healing problems	1	0	1	0
Proteinuria	1	1	0	0
Thrombocytopenia	1	1	0	0
Hypertension	1	1	0	0
Hematuresis	1	1	0	0

There were few studies focus on the efficacy of apatinib in advanced SS. Xie et al[30] reported as a second-line or further-line option, apatinib was administrated for six patients with advanced SS following anthracycline-based chemo-resistance. The median DOR was 5.2 months, and the best response was PR. Chen et al[31] reported a case of advanced SS. Apatinib was administrated as a third-line treatment. The PFS and OS were 7.0 and 8.5 months, respectively. And no grade 3 or 4 side effects were observed. However, compared with previous studies, our data show a significant improvement in PFS (13.1 months) and OS (15.5 months), with similar DOR (7.7 months). And, apatinib shows relatively less and lower-grade AEs, when compared to pazopanib and regorafenib.[15,17,30] Therefore, in our study, most patients received apatinib 750 mg once daily for body surface area (BSA) >1.5.[30] The initial dose was relatively high, compared with the previous study. Additionally, although chemotherapy agents primarily act in the cell cycle, SS tumor cells are selected for insensitive chemotherapy, which contributes to the formation of chemotherapy-resistant SS. In the previous study, six advanced SS cases only had a median DOR of 5.2 months with apatinib treatment following

Table 4 Targeted Agents for Advanced SS

Drug (Reference)	Year of Publication	No. of Patients	Prior Chemotherapy	Target Therapy Protocol	Best Response	Clinical Outcome
Sorafenib[23]	2009	12	Yes	Sorafenib 400mg twice per day	Six SD Six PD	Median PFS=2.5m, Median OS=10.3m
Pazopanib						
Sleijfer, S. et al[24]	2009	38	Yes	Pazopanib 800mg	–	3-month PFS rate=49%, Median PFS=161d
Van der Graaf, W. T. et al[15]	2012	44	Yes	Pazopanib vs Placebo	-	Median PFS=4.6m, Median OS=12.5m
Yoo, K. H. et al[16]	2015	4	Yes	Pazopanib 800mg	Two PR	Median PFS=7.7m, Median OS=9.4m
Nakamura, T. et al[25]	2016	18	Yes	Pazopanib 200/400/600800mg	Two PR Ten SD Four PD	Median PFS=16.4w, Median OS=10.6m, 6-Month PFS rate=42.8%, 1-Year OS rate=41.4%
Gelderblom, H. et al[26]	2017	24	Yes	Pazopanib 200/400/600800mg	Two PR Ten SD Four PD	Median treatment Duration=5.1m
Jee Hung Kim et al[27]	2019	3	Yes	Pazopanib vs Gemcitabine/Docetaxel	One PR One SD One PD	Median PFS=3.1m
Regorafenib						
Brodowicz, T. et al[28]	2015	26	Yes		One PR	22
Mir, O. et al[17]	2016	13	Yes	Regorafenib vs Placebo	One PR Ten SD Two PD	Median PFS=5.6m, Median OS=13.4m, 6-Month PFS rate=38%, 6-Month OS rate=77%
Berry, V. et al[3]	2017	13	Yes	Regorafenib vs Placebo	-	Median PFS=4.0m; Median OS=13.4m
Brodowicz, T. et al[29]	2018	13	Yes	Regorafenib vs Placebo	One PR Ten SD Two PD	Median PFS=3.8m, Median OS=13.4m,
Apatinib						
Xie et al[30]	2018	6	Yes	Apatinib 500mg	PR	Median DOR=5.2m
Chen et al[31]	2019	1	Yes	Apatinib 500mg	SD	PFS=7m, OS=8.5m
Current study	-	21	Yes	Apatinib 750mg	PR	Median PFS=13.1m, Median OS=15.5m,

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not achieved; ORR, objective response rate (including the percentage of CR and PR); PFS, progression-free survival; OS, overall survival; OSR, overall survival rate.

poor response to at least two circles of anthracycline-based chemotherapy.[30] However, van der Graaf et al[15] reported pazopanib improved the median PFS (5.6 months) and OS (13.4 months) in advanced SS patients who previously had one circle chemotherapy. So apatinib was administered after the poor response of one circle chemotherapy in our study, with the notable result of nine PR and eight SD (Figure 4). Therefore, we speculate the improvement of median OS, especially PFS, is extensively influenced by the relatively high dose and advanced treatment, when compared to early trials.[15,17,30]

For the AEs, previous studies reported the most common toxicities were hand-foot skin reaction, fatigue, rash or desquamation, and hypertension for advanced STS.[20,30] In our cases, the most common AEs in our study were hand-foot skin reaction (7/21[33.3%]), oral ulcers (7/21

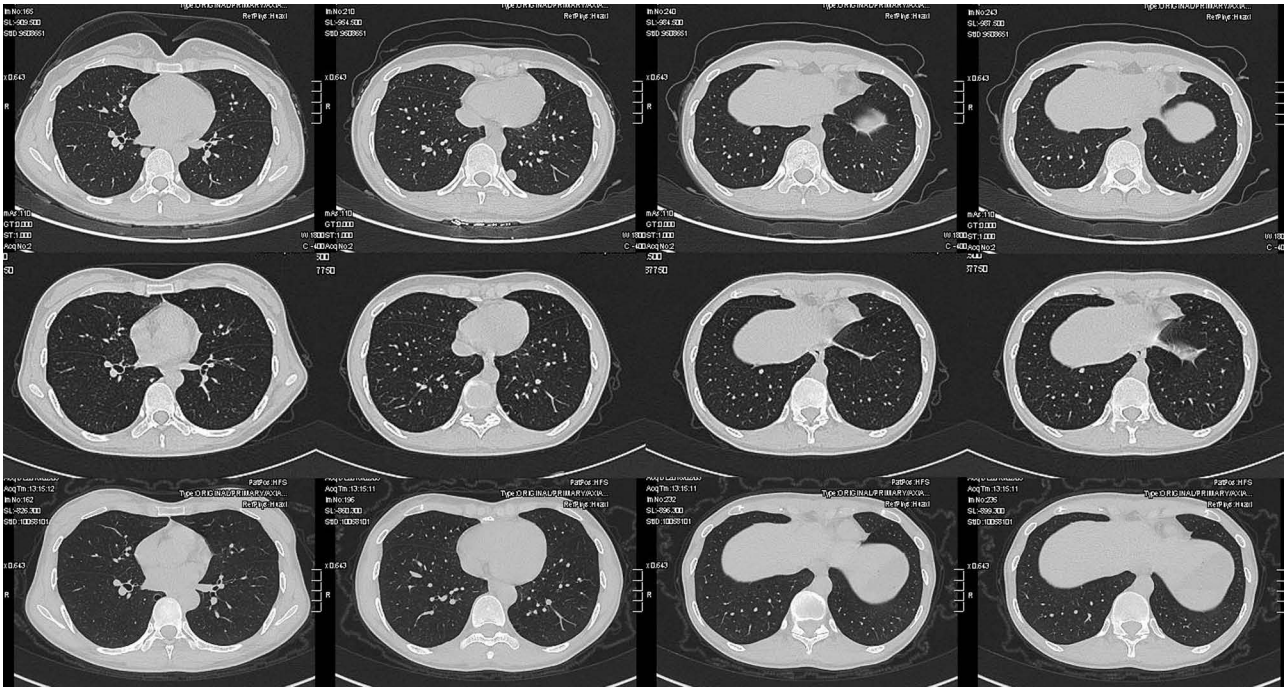


Figure 4 The patient with partial response showing response to the treatment with apatinib.

[33.3%]), and vomiting (6/21[28.6%]). Then, only one patient had to discontinue apatinib because of hand-foot skin reaction, and one patient received closed chest drainage following grade 4 pneumothorax. No other grade 3/4 toxicities were detected. However, as mainstream care for patients with non-adipocytic sarcomas, the use of pazopanib had induced several grade ≥3 toxicities including neutropenia, thrombocytopenia, pulmonary embolism, and nausea.[26,27] Rapid and fatal acute heart failure had been even reported which induced by pazopanib.[35] The quality of life was significantly decreased in SS patients who administrated pazopanib because of AEs (ie, diarrhea, anorexia, nausea, vomiting, and asthenia).[15] Meanwhile, three of all the 14 patients discontinued regorafenib for the regorafenib-induced toxicities.[17] Hypertension, hand-foot skin reaction, and asthenia were the most common grade ≥3 toxicities for STS patients with regorafenib.[17] However, the overall toxicity and safety of apatinib were relatively better in advanced SS patients, when compared to pazopanib and regorafenib.

The study has several limitations. Firstly, it was a retrospective review of one institution, and there was no control for comparison. Secondly, we only enrolled 21 patients with a median follow-up time of 15.2 months. Moreover, regardless of the encouraging results, our study is lacking the relevant research on the mechanism of molecular biology in each patient. When making histological diagnose, our institution just concluded the typical immunohistochemical features of SS including: CD99 (+), vimentin (+), WT-1 (+), CK (-), HBME1 (-), TTF1 (-), Napsin A (-), p16 (-), NSE (-), Chromogranin A (-), Bcl-2 (+). However, our results are highly variable, whether the immunohistochemical features will impact on the clinical outcomes is unknown. Moreover, apatinib is known as a VEGFR-TKI, but the definite mechanism of antitumor activity remains a question. Therefore, prospective studies with multicenter and large sample are needed for further evaluating the efficacy and safety of apatinib.

Conclusions

In our study, the advanced SS patients with poor response to anthracycline-based chemotherapy revealed favorable short-term outcomes after using apatinib. Although the evidence level of this study seems preliminary, patients treated with apatinib indeed had a significant improvement on OS, and particularly on PFS. Meanwhile, the apatinib-induced toxicities were tolerable for most advanced SS patients. Apatinib was proved to be a potential second-line treatment option for advanced SS patients with chemo-resistance. Certainly, further long-term randomized controlled multicenter study with larger cases will fully determine the clinical application of apatinib in advanced SS.

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Disclosure

The authors report no conflicts of interest in this work.

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