Long-Term Efficacy and Safety of Anlotinib as a Monotherapy and Combined Therapy for Advanced Sarcoma

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Objective: To analyze the effectiveness of the long-term (> 12 months) administration of anlotinib as a monotherapy or combined therapy in patients with advanced sarcomas.

Methods: A retrospective analysis was conducted of patients with advanced sarcomas with measurable target lesions since 2018. Twenty-two of the patients had taken anlotinib regularly for > 12 months. The patients’ general information and the drug’s clinical efficacy and toxicity data were collected and statistically analyzed using RECIST 1.1 to measure the target lesions and tumor PFS time as the main endpoints. We used a swimmer plot to observe the drug’s efficacy and duration, and employed a waterfall plot to express the best treatment effect.

Results: The study included 14 male and 8 female patients, ranging in age from 14 to 75 (mean: 44.82) years. The primary diseases included alveolar soft part sarcoma, synovial sarcoma, leiomyosarcoma, and others. The metastasis sites were the lungs in fifteen cases, lymph nodes in four cases, and multiple sites in three cases. Fourteen patients had previously undergone chemotherapy. The current therapy protocol was oral anlotinib alone for nine cases, combination chemotherapy for nine cases, and combination immunotherapy (anti-PD-1) for four cases. The highest clinical efficacy was complete remission (CR) in four (18.18%) cases, partial response (PR) in five (22.73%) cases, and stable disease in 13 (59.09%) cases, with an odds ratio of response of 40.91%. The mean PFS for the CR, PR, and stable disease groups was 16.50, 14.50, and 29.31 months, respectively (p < 0.05). The main adverse effects included hand-foot syndrome, hypertension, and leukopenia.

Conclusion: Anlotinib monotherapy or combination therapy can be more effective and safer for certain advanced sarcomas, with more extended maintenance and acceptable side effects. Clinical efficacy at the CR and PR levels might predict the long-term PFS in certain advanced sarcomas.

Keywords: anlotinib, advanced sarcoma, targeted therapy, immunotherapy, clinical efficacy

Bone and soft tissue sarcomas (STS) are a group of malignant tumors derived from mesenchymal tissue and are characterized by high heterogeneity, complicated subtypes, high malignancy, and few available therapeutic methods. Moreover, most sarcomas are prone to metastasis through blood vessels to vital organs such as the lungs. The treatment of sarcoma is mainly based on extensive surgical resection, supplemented by perioperative radiotherapy, chemotherapy, and other treatments. For localized tumors, the 5-year survival rate can reach 70%–80%; however, advanced and metastatic sarcomas have a 5-year survival rate below 20%. The prognosis for patients with sarcomas remains poor, with a median overall survival (OS) of slightly more than 1 year. Therefore, exploring new methods for treating advanced sarcoma is a hot topic and challenging research area.
Angiogenesis plays an essential role in tumor growth and metastasis, and blocking this pathway is a strategy that has been successfully employed in clinically treating cancer.\(^6\) Receptor tyrosine kinases are among the most promising therapeutic targets and can be used to modulate cell proliferation, growth, angiogenesis, and metastasis in a wide range of cancers.\(^8\)–\(^{12}\)

Anlotinib (AL3818) is a novel oral receptor tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptors 2 and 3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptors \(\alpha\) and \(\beta\), c-Kit, and Ret,\(^{13}\) thereby exerting inhibitory effects on tumor growth and angiogenesis. A Phase I study of anlotinib by Sun et al\(^{14}\) demonstrated promising antitumor potential against STS. A multicenter, Phase II study by Chi et al (NCT01878448)\(^{15}\) investigated single-agent anlotinib in 166 patients with STS who experienced disease progression after anthracycline-based first-line chemotherapy. The progression-free survival (PFS) rate at 12 weeks was 68%, with an odds ratio of response (ORR) of 13% (95% confidence interval [CI], 7.6–18.0%), and the median PFS and OS were 5.6 and 12.0 months, respectively. The toxicity of anlotinib was acceptable or manageable in these patients and included hypertension and hand-foot syndrome. Anlotinib was approved and launched in the People’s Republic of China in May 2018, receiving approval in June 2019 as a second-line treatment for patients with advanced alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS), and other types of advanced STS after one line of a chemotherapy regimen containing anthracycline.

In addition to the apparent efficacy, the convenience of oral administration, and the acceptable adverse effects, studies have shown that anlotinib, together with chemotherapy and immunotherapy, has synergistic effects.\(^{16\,\,\,18}\) Clinical trials of this drug alone and in combination are being conducted. Anlotinib achieves its antitumor effect by inhibiting neovascularization of the microenvironment, a mechanism similar to that of metronomic chemotherapy administered in small doses over a long period; the longer the drug is administered, the longer its effectiveness.

This study investigated patients with sarcoma who took anlotinib for \(>12\) months. The study aimed to explore the safety and efficacy of the long-term use of anlotinib and analyzing the factors that influence and possibly predict the long-term efficacy of anlotinib. Additionally, we sought to provide potential therapeutic protocols for the subsequent treatment of advanced sarcomas.

### Clinical Data

#### Patient Population and Data Collection

We collected the clinical data of patients diagnosed with advanced sarcomas who were ineligible for surgery at our hospital from June 2018 to December 2020. The inclusion criteria were as follows: 1) age \(\geq 12\) years; 2) confirmed diagnosis of bone and STS involving the limbs and trunk according to immunohistochemical and genotypic analysis performed by pathologists in our hospital; 3) unresectable or metastatic tumor lesions unsuitable for curative therapy; 4) maintaining \(\geq 12\) months of anlotinib therapy; 5) at least one measurable tumor as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1); 6) having previously taken other TKIs; and 7) with or without other treatments, such as chemotherapy and immunotherapy. The exclusion criteria were 1) unconfirmed pathological diagnosis, and 2) poor compliance, and irregular medication or follow-up.

Clinical data were gathered and recorded throughout the study, including sex, age, histological characteristics, medication methods, primary sites of the sarcomas, metastatic locations, clinical efficacy (PFS), and adverse events (AEs). Our study complies with the Declaration of Helsinki.

#### Therapeutic Schemes

The patients were initially administered anlotinib (provided by the Zhengda Tianqing Pharmaceutical Company) in 21-day cycles at a dosage of 12 mg/day from day 1 to day 14. Chemotherapy was performed for approximately 6 cycles, using a single agent of doxorubicin (60–90 mg/m\(^2\)) or ifosfamide (10 g/m\(^2\)) and then maintained with anlotinib. Anti-PD-1 was administered every 3 weeks. The therapy was continued until the disease progressed or unacceptable AEs occurred. The AEs were classified and graded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.\(^{19}\) The dose could be reduced or temporarily suspended according to the patient’s tolerance. The initial dosage of 12 mg/day of anlotinib was allowed to be reduced to 10 mg/day and then to

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8 mg/day after less than 1 week of discontinuation. When the AEs became tolerable, a higher dosage could be readministered.

**Assessment of Safety and Toxicity**
Radiological assessment of the target lesions by computed tomography scans and magnetic resonance imaging was performed at baseline, 1–2 months after the start of therapy, and then every 12 weeks if clinically indicated. The results were analyzed according to the RECIST (version 1.1). The dual primary endpoint of the objective response rate and median PFS was assessed during the study period. The best responses were recorded from the first efficiency assessment to the time of progression after therapy. The responses were further categorized into either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The ORR was defined as the percentage of patients who experienced CR and PR. PFS was calculated from the start of treatment to the first documented disease progression or death, whichever occurred first. AEs were graded and recorded using CTCAE.

**Statistical Analysis**
The quantitative variables are presented as the median (range) or frequency (percentage). The PFS and corresponding 95% CIs were calculated using the Kaplan–Meier method. Statistical analyses were performed using SPSS version 21.0 (IBM, Chicago, IL), employing a swimmer plot to observe the drugs’ efficacy and duration and a waterfall plot to express the best treatment effect.

**Results**

**General Information**
The study included 22 patients (14 male and 8 female), ranging in age from 14 to 75 years (mean age: 44.82 years). The primary diseases included ASPS in five cases, synovial sarcoma (SS) in four cases, leiomyosarcoma in three cases, epithelioid sarcoma (ES) and undifferentiated pleomorphic sarcoma (UPS) in two cases each, and clear cell sarcoma (CCS), rhabdomyosarcoma, angiosarcoma, fibrosarcoma, pleomorphic liposarcoma and osteosarcoma in one case each (Figure 1). The target observed lesions (confirmed by pathologists) included 15 cases of pulmonary nodules, four cases of enlarged lymph nodes, and three cases of multiple metastases.

The number of treatment lines was as follows: five cases with first-line therapy (with previous no therapy), nine cases with second-line therapy (with a previous first-line therapy), six cases with third-line therapy (with a previous second-line therapy), and two cases with fourth-line therapy (with a previous third-line therapy) or above. There were 14 cases with previous chemotherapy and two cases with antiangiogenic targeted drug therapy. Except for three patients, nineteen cases had unplanned surgery in other general hospitals and reoperation in our department within three months. The surgical margin was Ro in seventeen cases and R1 in five cases (close to vital vessels). The previous chemotherapy protocol included single or combined agents of doxorubicin (60–90 mg/m2), ifosfamide (10 g/m2), gemcitabine (1000 mg/m2), docetaxel (70–75 mg/m2) in most sarcomas. Some special drugs such as methotrexate (8–12 g/m2) and cisplatin (100 mg/m2) in OS, vincristine (1.4 mg/m2) and cyclophosphamide (1000 mg/m2) in RMS was applied. The previous targeted drug was apatinib (500 mg/day).

The choice of treatment modality was as follows: nine cases were treated with oral anlotinib alone. The primary diseases included ASPS in two cases, SS in two cases, and CCS, UPS, leiomyosarcoma, osteosarcoma, and liposarcoma in one case each. Nine cases were treated with anlotinib combined with chemotherapy, including two cases of SS, two cases of leiomyosarcoma, and one case each of ES, UPS, angiosarcoma, rhabdomyosarcoma, and fibrosarcoma. There were four cases of anlotinib combined with anti-PD-1 immunotherapy, including three cases of ASPS and one case of ES (Table 1).

**Tumor Response**
There were four cases of CR (18.18%), including two cases of anlotinib combined with anti-PD-1 therapy (one case each of ASPS and ES) and one case of anlotinib monotherapy (SS) or combined chemotherapy (ES) (Figure 1). Two of these
patients were treated with second-line therapy, one was treated with third-line therapy, and one was treated with fourth-line therapy (Figure 2).

There were five cases (22.73%) of PR, including one case of anlotinib monotherapy (liposarcoma), three cases of combination chemotherapy (one case of UPS, rhabdomyosarcoma, and fibrosarcoma each), and one case of combination anti-PD-1 therapy (ASPS) (Figure 1). One patient underwent first-line therapy, two underwent second-line, one underwent third-line, and one underwent fifth-line therapy (Figure 2). The remaining 13 cases maintained SD during therapy (59.09%; ORR, 40.91%).

**Efficacy Duration of the Study**

The earliest occurrence of CR was 1 month after the start of therapy, and the latest time reached was 9 months after the start of therapy. Most target lesions reached a period of PR and then turned to CR. Twenty-five months was the longest CR maintained, and two cases of CR persisted until the end of the study. The CR time lasted a mean of 13.50 months, and the PFS was 16.50 months in this patient group.

PR appeared 1–2 months after therapy in five patients, with four cases of PR persisting until the end of the study. The last period was 9–17 (mean: 12.20) months, and the PFS was 14.50 months for the PR patients.

The longest SD duration was 35 months, and the shortest was 9 months. Consistent efficiency was maintained in four cases at the last follow-up. The SD lasted for approximately 17.62 months, and the PFS was 29.31 months. There was no statistically significant difference in PFS between the three groups (p = 0.059).
| No. | Gender | Age  | Pathological Diagnosis | Primary Tumor Surgery | Lines of Therapy | Drug Protocol | Clinical Effect | PFS Disease Progress | Current Status | AEs                                                                 |
|-----|--------|------|------------------------|-----------------------|------------------|---------------|----------------|-------------------|----------------|----------------------------------------------------------------------|
| 1   | Male   | 36   | ASPS                   | Ro                    | 3                | A             | SD             | 24                | Yes            | Stable Hypertension of grade 1                                        |
| 2   | Male   | 23   | ASPS                   | Ro                    | 4                | A+I           | CR             | 12                | Yes            | Stable Hand-foot syndrome of grade 1                                  |
| 3   | Male   | 36   | SS                     | Ro                    | 2                | A+C           | SD             | 16                | No             | Progression Hypertension of grade 1                                  |
| 4   | Male   | 49   | ES                     | Ro                    | 2                | A+I           | CR             | 23                | No             | Stable Hypothyroidism, weakness and anorexia of grade 3, hand-foot syndrome of grade 2 |
| 5   | Male   | 68   | CCS                    | Ro                    | 1                | A             | SD             | 13                | No             | Death None                                                          |
| 6   | Male   | 38   | UPS                    | Ro                    | 3                | A+C           | PR             | 9                 | No             | Death None                                                          |
| 7   | Male   | 40   | SS                     | Ro                    | 2                | A+C           | SD             | 24                | No             | Progression Leukopenia, hypertension and hand-foot syndrome of grade 1 |
| 8   | Female | 19   | ASPS                   | R1                    | 1                | A             | SD             | 38                | Yes            | Stable Hypertension and hand-foot syndrome of grade 1 and wound rupture, pneumothorax |
| 9   | Stable | 14   | ES                     | R1                    | 2                | A+C           | CR             | 26                | Yes            | Progression Hand-foot syndrome of grade 1                             |
| 10  | Female | 37   | LMS                    | Ro                    | 1                | A+C           | SD             | 12                | No             | Progression None                                                   |
| 11  | Male   | 42   | RMS                    | R1                    | 2                | A+C           | PR             | 11                | Yes            | Surgery Leukopenia and febrile neutropenia of grade 3               |
| 12  | Female | 47   | FS                     | Ro                    | 2                | A+C           | PR             | 16                | No             | Stable Leukopenia and hand-foot syndrome of grade 1                 |
| 13  | Female | 54   | LMS                    | Ro                    | 3                | A+C           | SD             | 35                | Yes            | Stable Hypertension of grade 2, hand-foot syndrome of grade 1        |
| 14  | Male   | 46   | SS                     | Ro                    | 3                | A             | CR             | 26                | No             | Progression Hand-foot syndrome grade 1                               |
| 15  | Male   | 75   | LMS                    | R1                    | 1                | A             | SD             | 17                | No             | Progression Hypertension of grade 1                                  |
| 16  | Male   | 50   | UPS                    | Ro                    | 2                | A             | SD             | 10                | No             | Progress None                                                      |
| 17  | Male   | 57   | OS                     | Ro                    | 2                | A             | SD             | 17                | No             | Death Hand-foot syndrome of grade 1                                  |
| 18  | Female | 41   | SS                     | Ro                    | 2                | A             | SD             | 16                | No             | Progression Weakness and anorexia f grade 2                           |
| 19  | Male   | 63   | ASPS                   | Ro                    | 1                | A+I           | PR             | 18                | No             | Stable Hypertension of grade 1,                                     |
| 20  | Female | 42   | ASPS                   | Ro                    | 3                | A+I           | SD             | 11                | Yes            | Stable None                                                        |
| 21  | Female | 62   | LS                     | R1                    | 5                | A             | PR             | 12                | No             | Stable None                                                         |
| 22  | Female | 47   | AS                     | Ro                    | 3                | A+C           | SD             | 11                | No             | Progression Leukopenia of grade 1                                   |

**Abbreviations:** ASPS, alveolar soft part sarcoma; SS, synovial sarcoma; LMS, leiomyosarcoma; ES, epithelioid sarcoma; UPS, undifferentiated pleomorphic sarcoma; CCS, clear cell sarcoma; RMS, rhabdomyosarcoma; AS, angiosarcoma; FS, fibrosarcoma; LS, pleomorphic liposarcoma; OS, osteosarcoma; A, anlotinib; C, chemotherapy; I, immunotherapy; CR, complete response; PR, partial response; SD, stable disease.
Common toxicities included hand-foot syndrome in nine cases (40.91%), hypertension in six cases (27.27%), leukopenia in four cases (18.18%), and weakness and anorexia in two cases (9.09%). The grade 3–4 severe AEs included febrile neutropenia in one case, weakness due to hypothyroidism in one case, and wound-healing difficulty with ulcers in one case (Table 1).

**Toxicities**

Common toxicities included hand-foot syndrome in nine cases (40.91%), hypertension in six cases (27.27%), leukopenia in four cases (18.18%), and weakness and anorexia in two cases (9.09%). The grade 3–4 severe AEs included febrile neutropenia in one case, weakness due to hypothyroidism in one case, and wound-healing difficulty with ulcers in one case (Table 1).
Typical Cases (See Figure 3)

Case 1 was a 23-year-old male patient with a diagnosis of ASPS. After a previous third-line therapy, the target lesion was cavitated, and complete remission (CR) was achieved after 3 months of anlotinib combined with anti-PD1 therapy and maintained continuously for approximately 19 months. (see Figure 3①)

Case 2 was a 49-year-old male patient with epithelioid sarcoma (ES). After another tyrosine kinase inhibitor (TKI)-targeted first-line drug therapy, the target lesion gradually disappeared. CR was achieved after 1 month of anlotinib combined with anti-PD1 therapy and maintained for approximately 23 months with ongoing efficacy. (see Figure 3②)

Case 3 was a 46-year-old male patient with synovial sarcoma (SS). After previous second-line chemotherapy, cavitation of the target lesion appeared after 6 months of oral anlotinib. However, the tumor progressed again and continued for approximately 26 months. (see Figure 3③)

Case 4 was a 62-year-old female patient with liposarcoma. After multiple lines of chemotherapy, partial response (PR) was achieved for the target lesion after anlotinib monotherapy for 12 months, and the efficacy was maintained. (see Figure 3④)

Case 5 was a 38-year-old male patient with undifferentiated pleomorphic sarcoma (UPS). After 2 lines of therapy, the target lesion was kept at PR after anlotinib combined with chemotherapy for approximately 9 months; however, mass enlargement led to progressive disease (PD) at 12 months of therapy. (see Figure 3⑤)

Case 6 was a 47-year-old female patient with metastatic fibrosarcoma of the rib. After first-line chemotherapy, the target lesion shrank after 1 month, and PR was sustained for 16 months with the protocol of anlotinib combined with chemotherapy. The efficacy is currently maintained. (see Figure 3⑥)

Case 7 was a 42-year-old female patient with ASPS. After 2 lines of therapy, the target lesion achieved stable disease (SD) status with the protocol of anlotinib combined with anti-PD1 therapy for approximately 12 months. (see Figure 3⑦)
Case 5 was a 38-year-old male patient with a diagnosis of UPS. After two lines of therapy, the target lesion was maintained at a PR after anlotinib combined with chemotherapy for approximately 9 months; however, mass enlargement led to PD at 12 months of therapy. (see Figure 3(5))

Case 6 was a 47-year-old female patient with a diagnosis of metastatic fibrosarcoma of the rib. After first-line chemotherapy, the target lesion shrunk after 1 month, and PR was sustained for 16 months with the protocol of anlotinib combined with chemotherapy. The efficacy is currently being maintained. (see Figure 3(6))

Case 7 was a 42-year-old female patient with a diagnosis of ASPS. After two lines of therapy, the target lesion achieved SD status with the protocol of anlotinib combined with anti-PD-1 therapy for approximately 12 months. (see Figure 3(7))

**Discussion**

Bone sarcoma and STS account for approximately 1% of adult and 15% of pediatric malignant tumors, with a survival rate of only 20–40% for bone sarcoma and 35% for STS before the use of chemotherapy. Since the 1970s, chemotherapies have been applied and have achieved significantly better outcomes for sarcoma, with a 5-year survival rate of 60–80% when accompanied by surgical resection. Surgical resection can cure certain sarcomas, and better outcomes can be achieved when combined with chemotherapy or radiation. However, the systemic toxicity of and multidrug resistance to chemotherapy has limited the maximum applicable dosage, which is one of the major reasons for local recurrence and treatment failure. Metastatic lesions are detected in approximately 10% of patients with sarcomas during the first visit. Moreover, metastatic disease occurs in 25% of patients with sarcomas after the radical treatment of primary tumors. Therefore, there is an urgent need for new treatments for sarcomas.

Neovascularization in tumor tissues creates a lifeline for developing tumor cells. Through continuous tumor angiogenesis, nutrients are continuously supplied and simultaneously provide vascular channels for the growth, infiltration, and metastasis of tumor cells. Vascular endothelial growth factor (VEGF) is expressed in many tumors as an important regulatory factor in tumor angiogenesis. Since pazopanib, one of the anti-angiogenesis-targeted drugs acquired its indication for the second-line treatment of sarcomas, more and more multikinase inhibitors (MTKI), such as sorafenib, regorafenib, cabozantinib, and lenvatinib, all with non-specific activities targeting VEGF receptors, have been proved effective in sarcomas. Among which regorafenib and anlotinib have achieved good results. Nevertheless, anlotinib is the only drug currently indicated for sarcoma in China. Previous studies have shown that anlotinib has satisfactory effectiveness in certain advanced STS, with fewer side effects, ease of use, and acceptance by patients. The most common grade 3 and 4 AEs of anlotinib are hypertension (4.8%), increased triglyceride levels (3.6%), and pneumothorax (2.4%). This treatment is generally well tolerated as a single or combination therapy.

However, the main problems with anti-angiogenesis-targeted drugs are short duration with secondary drug resistance, and studies are mostly limited to patients in advanced stages after multiple lines of therapy, with relatively few reports of patients with long-term effectiveness. Given that tumor angiogenesis is only one pathway, the complex mechanism of tumor growth implies that multi-pathway and multidrug combinations can be more effective in treating sarcomas and achieving long-lasting efficacy. Wang et al. reported that a low concentration (1 mM) of anlotinib-promoted cisplatin (DDP)-induced cell apoptosis and increased the inhibitory effects of DDP on the proliferation of osteosarcoma cells. Compared to anlotinib or DDP alone, the combination notably reduced tumor weight and volume in vivo. Clinical studies have increasingly shown that anti-angiogenic targeted agents in combination with radiotherapy, chemotherapy, or immunotherapy can be employed for advanced sarcomas, with significant efficacy, a higher ORR, and longer duration than that of single agents.

A study retrospectively collected medical data from 32 patients with advanced/metastatic STS. The patients underwent chemotherapy and anlotinib plus anlotinib maintenance therapy. The results showed that the combination of chemotherapy and anlotinib could improve the survival rate of patients with advanced/metastatic STS and was well tolerated. Liu et al. analyzed the data from 21 adults with unresectable or metastatic STS who were retrospectively diagnosed. The results indicated that switching maintenance therapy with anlotinib is a promising strategy for treating patients with unresectable or metastatic STS who have undergone chemotherapy.

Our study employed a retrospective survey of patients who used anlotinib for more than 1 year. The ratio of male to female patients was 1.5. The drug was shown to be in targeted-drug-sensitive diseases, such as ASPS and SS, immunotherapy-
sensitive diseases, such as ES and ASPS, and chemotherapy-sensitive diseases, such as leiomyosarcoma and rhabdomyo-
sarcoma. Four patients achieved CR with the disappearance of the metastatic lesions or thin-walled cavities. However, as the
follow-up is extended, certain disappeared lesions reappear and progress rapidly, a phenomenon that might be related to drug
resistance or insufficient antitumor effect. Five patients achieved PR, which manifested as a reduction in the diameter of the
target lesion, usually about 1 month after the therapy, and was maintained for approximately 9–17 months. The disease control
rate of this patient group was 100%, and the ORR was 46%. The results indicate that tumor disappearance or significant
shrinkage might indicate long-term tumor control. However, there was no positive correlation between PFS and ORR. In this
study, the longest SD duration was 35 months (mean, 17.62 months), the CR duration was 13.50 months, and the PR duration
was 12.20 months. The PFS reached 16.50, 14.50, and 29.31 months for the CR, PR, and SD groups, respectively, with no
statistically significant difference. Therefore, maintaining tumor regression for a longer period is an important issue for the
future.

In our study, the sarcomas that were most effectively treated with targeted drugs alone or in combination were ASPS,
SS, and ES. The common feature of these three subtypes is abundant tumor vascularity, which is a relatively straightfor-
ward anti-angiogenic effect observed in previous studies. ASPS achieved CR in combination with immunotherapy,
ES showed CR in combination with immunotherapy (one case) or chemotherapy (one case), and single-agent anlotinib
achieved CR in only one case of SS. Therefore, anti-angiogenesis treatment in combination with other therapeutic
measures especially immunotherapy may be necessary to obtain better outcomes.

The primary metronomic chemotherapy methods employ long-term low-dose drugs such as methotrexate and
cyclophosphamide for advanced sarcomas. This mechanism involves inhibiting the formation of tumor neovascular-
ization, which leads to tumor death. As anlotinib has clear anti-VEGF and neovascularization properties, it should,
theoretically, meet or exceed the effects of metronomic chemotherapy when used long-term at low doses. The current
study suggests that the relatively short PFS is related to the saturation of TKI-related targets in tumor cells or the opening
of other tumor pathways, which leads to further elevation of tumor cell activity. The oral duration of anlotinib in this
study was more than 1 year in all cases, but its effectiveness was maintained in only eight (36.37%) patients at the last
follow-up, as shown in the swimmer plot. Tumor resistance remains a significant impediment to the prolonged use of
TKI-targeted agents. Therefore, changing the dosing strategy or adjusting the treatment sequence of various drugs
could lead to better and longer-lasting clinical effects in certain patients with sarcoma.

The main AEs of the long-term use of anlotinib are hypertension, hand-foot syndrome, and weakness. Myelosuppression is
the main complication when chemotherapy is added, and hypothyroidism can appear after immunotherapy is combined.
However, few severe AEs were observed, which might be due to the patients’ good physical condition, timely management of
complications, reasonable downward dose adjustment, and short discontinuation of the targeted drugs. However, rare
complications do exist as a result of prolonged administration of drugs, including wound ulceration and difficulty in healing,
the management of which requires the discontinuation of the targeted drugs, intensive wound dressing changes, and further
debridement, if necessary. The AEs of single-agent or combined chemotherapy and immunotherapy in this group did not
exceed the severity reported in the available literature.

The novelty of the current study included that we confirmed the feasibility, effectiveness, and safety of the long-term
use of anlotinib, providing a new treatment method for the first time. The search for new low-toxic and high-efficiency
targeted drugs and metronomic chemotherapy to achieve tumor control is a new direction for treating STS. Combining
more drugs or therapeutic methods to achieve rapid tumor shrinkage and proper maintenance might be an effective means
to achieve long-term control over advanced STS. The main limitations of this study are its small sample size, the use of
retrospective studies, and the inconsistency of the therapeutic agents. Large samples and prospective studies are needed
to confirm the long-term efficiency and adverse effects of combination therapies.

Although anlotinib monotherapy or a combination of other therapeutic methods seems to have advantages in
synergistic therapeutic effects and overcoming drug resistance, the disadvantages are that it increases the toxicity and
few patients can reach long-last effect. More specific immunotherapeutic agents such as immune checkpoint inhibitors
and monoclonal antibodies targeting the immune synapse between tumor and T lymphocyte are being tested in sarcomas.
However, the side effects for some patients can be harrowing. With high CD8 lymphocyte infiltration and high
expression of PD-1, PD-L1 is likely to be the best choice for anti-PD-1 therapy. In some special types of sarcomas,
such as synovial sarcoma, myxoid-round cell sarcoma, and malignant peripheral nerve sheath tumor (MPNST), consistently express cancer/testis antigens (CTAs) NY-ESO-1 or melanoma-associated antigen A4 (MAGE-A4), some new therapies such as chimeric antigen receptor T (CART) cell therapy are attractive. Antibody-drug conjugate (ADC) drugs against NY-ESO-1 have already demonstrated evidence of activity. Additionally, some new biomarkers such as neurotrophic tyrosine receptor kinase (NTRK), RANK-L, and corresponding drugs larotrectinib, denosumab have also been shown to affect certain sarcomas dramatically.

**Conclusions**

Anlotinib monotherapy or combination therapy can be more effective and safer for certain advanced sarcomas, with more extended maintenance and acceptable side effects. Anlotinib combined with anti-PD-1 therapy had better therapeutic efficacy for specific diseases such as alveolar soft part sarcoma and epithelioid sarcoma. Anlotinib combined with chemotherapy had therapeutic efficacy for synovial sarcoma, leiomyosarcoma, fibrosarcoma, and rhabdomyosarcoma. Clinical efficacy at the CR and PR levels might predict the long-term PFS in certain advanced sarcomas.

**Disclosure**

The authors report no conflicts of interest in relation to this work.

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