Retrospective review of safety and efficacy of anlotinib in advanced osteosarcoma with metastases after failure of standard multimodal therapy

Hanqing Li | Yang Li | Lei Song | Qiuchi Ai | Shuai Zhang

Abstract

Aim: To study the safety and efficacy of anlotinib, a multitargeted tyrosine kinase inhibitor, in the treatment of advanced osteosarcoma (OSS) with metastases.

Methods: We retrospectively studied patients with advanced OSS and metastases who received anlotinib treatment in our hospital from June 2018 to April 2020. All patients had received standard multimodal therapies, before taking anlotinib. Therapeutic doses of anlotinib were 12 mg for adults and 10 mg for children and adolescents once a day for 2 consecutive weeks, followed by a week of withdrawal. This 3-week cycle of treatment was continued until the tumor progressed rapidly or the patients failed to tolerate the side effects. Adverse drug reactions were recorded, and therapeutic efficacy was evaluated based on progression-free survival (PFS), disease control rate (DCR), overall survival (OS), and objective response rate (ORR).

Results: The median PFS was 9.8 ± 9 months, and the 6- and 10-month PFS rates were 73% and 33%, respectively. The median OS was 11.4 ± 6 months. No patients achieved complete response. After 6 months of treatment, the DCR and ORR were 80% and 13%, respectively. No drug-related deaths or Grade 4 adverse events occurred in the patients. Five patients (33%) had Grade 3 adverse events. The most common drug-related adverse events were hand-foot syndrome, fatigue, high blood pressure, anorexia, and pneumothorax.

Conclusions: Anlotinib had a modest therapeutic effect in patients with advanced OSS after the failure of standard treatment. The adverse events were mostly tolerable or relieved after treatment.

Keywords

anlotinib, efficacy, osteosarcoma, safety, targeted therapy

1 | INTRODUCTION

Sarcoma is a highly heterogenous malignant tumor originating from mesenchymal tissues and is divided into two types: soft tissue sarcoma (STS) and primary bone sarcoma (PBS). PBS mainly includes osteosarcoma (OSS), Ewing sarcoma, and chondrosarcoma. Among them, OSS is the most common primary malignant bone tumor. The peak incidence of OSS occurs in children and adolescents (< 24 years), affecting 4.4 per million people per year. The concept of neoadjuvant chemotherapy, the principle of surgical margins of extensive resection, and the promotion of treatment methods have been considered the basic treatment for OSS and have also made limb-salvage therapy one of the standard treatment methods for OSS. Limb-salvage therapy not only retains the patient’s limbs but also improves their long-term survival rate (> 5 years). However, there are still a large number of patients who fail surgery and are resistant to standard first-line
chemotherapeutic agents, eventually leading to treatment failure and distant metastases, such as lung and liver metastases. The most common metastatic site is the lungs, and the prognosis of metastasis is often very poor. Hence, there is an urgent need for a new and effective treatment method, especially for the treatment of metastatic OSS in the advanced stage.

In the process of studying the molecular mechanism of tumorigenesis, invasion, spread, and metastasis, researchers discovered related protein molecules and tried to use these protein molecules as attack targets to specifically inhibit the proliferation and spread of tumor cells. Molecular targeted therapy has become a hotspot in OSS research in recent years. The typical characteristic of a malignant tumor is continuous angiogenesis, which plays an important role in tumor invasion, growth, and metastasis. Thus, antiangiogenesis is considered to be a potential and important form of cancer treatment. Anlotinib, a new drug independently developed in China, is a small-molecule multitargeted tyrosine kinase inhibitor that effectively inhibits vascular endothelial cell growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor, stem cell growth factor receptor, and other kinase activities, thus inhibiting tumor blood vessel growth and consequently tumor growth. Anlotinib has shown good safety in third-line and above treatment of advanced non-small cell lung cancer and STS. The National Medical Products Administration (formerly the China Food and Drug Administration, CFDA) approved its listing on May 9, 2018. In this study, anlotinib was used as a single drug to treat metastatic advanced OSS after the failure of standard multimodal therapy to evaluate its safety and therapeutic efficacy, providing more clinical evidence for its ability to supplement and improve the treatment options for metastatic OSS.

2 | MATERIALS AND METHODS

A retrospective study including 15 patients with metastatic OSS who received at least one cycle of anlotinib in our center from June 2018 to April 2020 was carried out. All patients or immediate family members signed a written informed consent form and participated in this study voluntarily. Eligible patients had the following characteristics: measurable metastatic tumors in the lung and/or other regions; clear pathological diagnosis of OSS; complete pathology, imaging, and clinical records; had received standard chemotherapy drugs for OSS before anlotinib treatment, including doxorubicin, high-dose methotrexate, ifosfamide, and cisplatin, according to the National Comprehensive Cancer Network (NCCN) guidelines; and had completed at least one course of anlotinib treatment. The data derived from the medical history, previous treatment, clinical efficacy, and demographic characteristics of all patients were evaluated in this study.

2.1 | Treatment

Therapeutic doses of anlotinib for adults and for children and adolescents were 12 and 10 mg, respectively, once a day taken orally before breakfast for 2 consecutive weeks, followed by 1 week of withdrawal. This 3-week treatment cycle was repeated. If patients missed a dose, they were instructed to not take the missed dose if there were less than 12 h remaining before the next dose. Patients were followed to observe the performance of the medication, especially any adverse events related to the medication. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 issued by the National Cancer Institute. Patients with uncontrolled or intolerable adverse events had their anlotinib doses reduced to 10 or 8 mg. Moreover, patients were required to stop the medication when unacceptable serious adverse events or tumor progression occurred or when the patients refused to take the medication.

2.2 | Efficacy and safety assessments

The tumor response of the patients was evaluated by physical examinations, magnetic resonance imaging, and/or computed tomography (determined according to the clinical situation) every 2 months until the disease progressed. The evaluation indicators of the curative effect included progression-free survival (PFS), disease control rate (DCR), overall survival (OS), objective response rate (ORR), and complete response (CR). PFS was defined as the time from the beginning of anlotinib treatment to disease progression or death, and OS was defined as the duration from the first use of anlotinib to the last follow-up or death, whichever came first. DCR was considered to be the percentage of stable disease (SD), CR, and partial response (PR), whereas ORR was the percentage of PRs and CRs. PD, SD, CR, and PR were determined by professional physicians based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events related to the anlotinib treatment were evaluated according to the evaluation criteria for adverse drug events (version 4.0), from the beginning of the anlotinib application to at least 1 month after the last anlotinib application.

2.3 | Statistical analysis

In this study, therapeutic safety and survival analysis was performed for patients who had finished at least one cycle of anlotinib. Kaplan–Meier survival curves were used for OS and PFS estimations. All statistical data analyses were performed using SPSS for Windows (version 20.0, IBM, Armonk, NY).

2.4 | Ethics

This observational and retrospective study was approved by the ethics committee of the Southwest Hospital, the Third Military University (30 Gaotanyan Street, Shapingba District, Chongqing, China).

3 | RESULTS

3.1 | Patients and tumor characteristics

From June 2018 to April 2020, 15 OSS patients in our hospital received anlotinib treatment (Table 1). All patients had lung metastases before anlotinib treatment. The lung is the most common metastatic site in
| Age (years)/gender | Surgery before anlotinib | Chemotherapy before using apatinib | Radiotherapy before using anlotinib | Metastatic sites | Lung surgery | Response to anlotinib | OS (months) | PFS (months) |
|-------------------|--------------------------|------------------------------------|-----------------------------------|-----------------|-------------|---------------------|-------------|-------------|
| 15/female         | ADM + DDP + MTX + IFO   | No                                 | Lung                              | No              | PR          | 15                  | 15          |
| 10.8/male         | MTX + ADM + DDP + IFO   | No                                 | Lung                              | No              | SD          | 13                  | 13          |
| 20/male           | MTX + ADM + DDP + I     | No                                 | Lung                              | No              | PR          | 14                  | 14          |
| 11/female         | MTX + ADM + DDP + IFO + VP-16 | Yes                               | Lung                              | No              | SD          | 10                  | 8           |
| 15/female         | MTX + ADM + DDP IFO GEM + TXT | No                                 | Lung                              | No              | SD          | 10                  | 10          |
| 11.3/female       | MTX + ADM + DDP + IFO   | No                                 | Lung                              | No              | SD          | 9                   | 6           |
| 15/male           | MTX + ADM + DDP + IFO   | No                                 | Lung                              | No              | SD          | 11                  | 7           |
| 19/male           | MTX + ADM + DDP + IFO + VP-16 | No                                 | Lung                              | No              | SD          | 9                   | 5           |
| 15/male           | ADM + DDP + MTX + IFO   | No                                 | Lung                              | No              | PD          | 7                   | 3           |
| 11.6/female       | ADM + DDP + MTX + IFO   | No                                 | Lung + intra-calvarium            | No              | PD          | 13                  | 9           |
| 17/male           | MTX + ADM + DDP + IFO GEM + TXT | Yes                               | Lung                              | No              | SD          | 10                  | 7           |
| 16/male           | MTX + ADM + DDP + IFO   | No                                 | Lung                              | No              | SD          | 13                  | 10          |
| 14/female         | MTX + ADM + DDP + IFO   | No                                 | Lung                              | No              | PD          | 5.6                 | 2           |
| 17/male           | MTX + ADM + DDP + IFO + VP-16 | No                                 | Lung                              | No              | SD          | 9                   | 4           |
| 21/male           | MTX + ADM + DDP + IFO GEM + TXT | No                                 | Lung                              | No              | SD          | 12.7                | 9           |

Abbreviations: ADM, doxorubicine; DDP, cisplatin; GEM, gemcitabine; IFO, ifosfamide; MTX, methotrexate; OS, overall survival; PFS, progression free survival; PR, partial response; SD, stable disease; TXT, docetaxel; VP-16, etoposide.

OSS. The mean age of patients with OSS was 15.2 years (ranging from 10- to 21-year old), and 60% of the patients in this study were male. All patients received chemotherapy in accordance with the NCCN guidelines, with the main chemotherapeutic agents of methotrexate, cisplatin, doxorubicin, and ifosfamide. Eleven patients (73.3%) underwent limb salvage surgery before the anlotinib treatment, including extensive tumor resection and bone defect reconstruction. Four patients (26.7%) underwent amputation, and two patients received radiotherapy in other hospitals before amputation. Three patients underwent two surgeries, one of which was due to postoperative superficial incision infection, which was healed after debridement, and the other two patients underwent incision biopsies in another hospital. No local recurrence occurred in all 15 patients during follow-up. None of them underwent lung surgery. All patients received the anlotinib treatment for at least a month.

### 3.2 Therapeutic efficacy

In this study, the median follow-up time of the patients was 10.7 months. At the last follow-up, five patients (33%) died of tumor progression. Ten patients (66.6%) showed no progress after 6 months of anlotinib treatment. Three patients (20%) received anlotinib for more than a year. The median PFS time was 9.8 ± 9.9 months (95% confidence interval [CI]: 8.0–10.5). The 6- and 10-month PFS rates of the patients were 73% and 33%, respectively. The median OS time was 11.4 ± 6 months (95% CI: 10.3–12.5). None of the patients achieved CR. However, 10 patients (66.6%) had SD, and 2 patients (13%) had PR. After 6 months of follow-up, the DCR and ORR of the patients were 80% and 13%, respectively. Similar to other targeted drugs, clinical observations showed that an interruption of anlotinib treatment could lead to disease progression. Resuming anlotinib treatment may once again
Toxicity and safety

The drug toxicity was generally well tolerated by the patients. Anlotinib was approved by CFDA on May 8, 2018, for third-line and above treatment of lung cancer. Because the first targeted therapy drug, rituximab, was approved for clinical use by the United States Food and Drug Administration (US FDA) in 1997, there have been more drug trials specifically targeting OSS targets and immunotherapy. Angiogenesis is one of the important pathological characteristics of malignant tumors. It not only provides nutrition for the growth of tumor cells but also secretes growth factors to promote tumor cell proliferation and to play an important role in tumor growth, invasion, and metastasis. Thus, VEGF, which is involved in tumor angiogenesis, is an important antitumor target of drugs including bevacizumab, sunitinib, sorafenib, cediranib, and pazopanib. Among them, sorafenib has been recommended by the US FDA and the NCCN as a second-line drug for patients with relapsed and metastatic OSS. It prevents tumor blood vessel proliferation by inhibiting VEGF receptor 2 and PDFG-R-beta, thereby inhibiting tumor growth. The study results of Heymann et al. have shown that sorafenib is expected to reduce tumor growth and inhibit lung metastasis in an OSS model. Results of Grignani et al. in a phase II clinical trial of relapsed and unresectable OSS showed that the 4-month disease-free survival rate was 14% among all patients and 29% among patients with SD. However, sorafenib has not been approved in China for use in OSS patients. Moreover, the long-term application of sorafenib is very expensive. Most patients with OSS who have undergone surgery and multiple consecutive chemotherapies, especially those in developing western regions in China or other developing countries, cannot afford such a high medical cost. The cost burden of anlotinib is much lower than sorafenib, regorafenib, and pazopanib. Anlotinib was approved by CFDA on May 8, 2018, for third-line and above treatment of lung cancer.

In a multicenter, double-blind, randomized controlled phase III clinical trial study that included a total of 439 patients who were randomly assigned to an anlotinib group (296 cases) and a placebo group (143 cases) at a ratio of approximately 2:1, the OS time of the anlotinib group was significantly longer than that of the placebo group (9.6 vs. 7.1 months). Table 2 shows the adverse events occurred in at least one patient.

### Table 2: Drug-related adverse events that arose in at least one patient

| Adverse event                  | All, n (%) | Grade 1–2, n (%) | Grade 3–4, n (%) |
|-------------------------------|------------|-----------------|-----------------|
| Hand-foot syndrome            | 8 (53.3)   | 6 (40)          | 2 (13.3)        |
| Weight loss                   | 4 (26.7)   | 4 (26.7)        | 0 (0)           |
| Anorexia                      | 3 (20)     | 3 (20)          | 0 (0)           |
| Diarrhea                      | 5 (33.3)   | 5 (33.3)        | 0 (0)           |
| Dizziness                     | 1 (6.7)    | 1 (6.7)         | 0 (0)           |
| Proteinuria                   | 1 (6.7)    | 1 (6.7)         | 0 (0)           |
| Hypertension                  | 6 (40)     | 5 (33.3)        | 1 (6.7)         |
| Oral mucositis                | 2 (13.3)   | 2 (13.3)        | 0 (0)           |
| Fatigue                       | 4 (26.7)   | 4 (26.7)        | 0 (0)           |
| Rash acneiform                | 2 (13.3)   | 2 (13.3)        | 0 (0)           |
| Voice hoarse                  | 1 (6.7)    | 1 (6.7)         | 0 (0)           |
| Pneumothorax                  | 4 (26.7)   | 2 (13.3)        | 2 (13.3)        |
| Nausea/vomit                  | 2 (13.3)   | 2 (13.3)        | 0 (0)           |
| Aminotransferase/Bilirubin increase | 3 (20)   | 3 (20)          | 0 (0)           |

OSS is highly malignant and has a poor prognosis. It occurs in children and adolescents, seriously threatening their health and even life. In clinical practice, OSS manifests as local pain and swelling, sometimes accompanied by joint dysfunction. The manifestations are relatively insidious, and some may be found early due to pathological fractures caused by trauma. However, in other patients, some patients have had distant lung metastasis at the time of OSS diagnosis, and when distant metastasis of OSS occurs, the 5-year disease-free survival rate is less than 20%. The existing mainstream mode of treatment for OSS is preoperative neoadjuvant chemotherapy plus surgical resection plus postoperative adjuvant chemotherapy. The 5-year survival rate of patients has been greatly improved with the above treatment. However, no unified treatment plan is currently available for patients with advanced OSS and metastases who have failed the traditional standard treatment (i.e., surgery plus chemotherapy) in China and other countries. The prognosis of these patients is usually poor. Thus, it is imperative to explore new safe and effective treatment methods and strategies for OSS.

Molecular targeted therapy has become one of the hotspots in tumor therapeutic research in recent years. Because the first targeted therapy drug, rituximab, was approved for clinical use by the United States Food and Drug Administration (US FDA) in 1997, there have been more drug trials specifically targeting OSS targets and immunotherapy. Angiogenesis is one of the important pathological characteristics of malignant tumors. It not only provides nutrition for the growth of tumor cells but also secretes growth factors to promote tumor cell proliferation and to play an important role in tumor growth, invasion, and metastasis. Thus, VEGF, which is involved in tumor angiogenesis, is an important antitumor target of drugs including bevacizumab, sunitinib, sorafenib, cediranib, and pazopanib. Among them, sorafenib has been recommended by the US FDA and the NCCN as a second-line drug for patients with relapsed and metastatic OSS. It prevents tumor blood vessel proliferation by inhibiting VEGF receptor 2 and PDFG-R-beta, thereby inhibiting tumor growth. The study results of Heymann et al. have shown that sorafenib is expected to reduce tumor growth and inhibit lung metastasis in an OSS model. Results of Grignani et al. in a phase II clinical trial of relapsed and unresectable OSS showed that the 4-month disease-free survival rate was 14% among all patients and 29% among patients with SD. However, sorafenib has not been approved in China for use in OSS patients. Moreover, the long-term application of sorafenib is very expensive. Most patients with OSS who have undergone surgery and multiple consecutive chemotherapies, especially those in developing western regions in China or other developing countries, cannot afford such a high medical cost. The cost burden of anlotinib is much lower than sorafenib, regorafenib, and pazopanib. Anlotinib was approved by CFDA on May 8, 2018, for third-line and above treatment of lung cancer.

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6.3 months), the PFS was significantly prolonged (5.4 vs. 1.4 months), and the ORR and DCR were heightened (9.18% vs. 7.0% and 80.95% vs. 37.06%, respectively), with all showing significant improvement. Based on the excellent efficacy and safety of anlotinib in the treatment of a variety of malignant tumors, we have gradually begun to try the second- and third-line treatments for metastatic Oss. Tian et al. retrospectively studied 110 patients who received apatinib or anlotinib alone, including 32 Oss and 78 STS. In the treatment of Oss, ORRs were 15.79% (3/19) in the apatinib group and 7.69% (1/13) in the anlotinib group, and DCRs were 63.16% (12/19) in the apatinib group and 30.77% (4/13) in the anlotinib group. The m-PFSs were 4.67 ± 3.01 months in the apatinib group and 2.67 ± 1.60 months in the anlotinib group. These results indicate that both apatinib and anlotinib are effective in the treatment of sarcoma. However, the specific efficacy and adverse events are based on the tissue type of the sarcoma. For metastatic Oss, apatinib seems to be more effective than anlotinib. Nevertheless, in our current study, the PFS was 9.8 ± 9 months, and the OS was 11.4 ± 6 months. Ten patients (67%) exhibited SD, and 2 patients (13%) had PR. Comparing the results of the average PFS of sorafenib and apatinib, anlotinib seems to be superior to apatinib and sorafenib in the treatment of metastatic Oss, indicating that anlotinib can be used as a potential new treatment option. However, the number of patients in our study is relatively small, and a larger number of patients are needed to further confirm this observation. Compared with other literature reports, the patients in our study were younger. If the anti-angiogenic drugs such as anlotinib are more effective for children or adolescents, we do not know and need clinical comparison trial to further evaluate the value of anlotinib in the treatment of advanced Oss patients of different ages. In addition, based on previous literature, an antitumor-targeted drug with more targeted receptors has better clinical effects. Anlotinib is a multitarget drug that inhibits multiple receptors and has shown certain advantages in the treatment of malignant tumors. Our research also obtained evidence in support of its clinical efficacy. Most patients’ tumors were under control after taking the medication, and some patients benefited for a long time, but none achieved CR. Anlotinib was effective in treating metastatic Oss, although its underlying mechanism needs to be clarified by further study.

Importantly, in some patients with PR and SD, we found that tumor cavities formed in lung metastases for unknown reasons. It is possible these cavities were caused by ischemic necrosis of tumor cells after tumor angiogenesis was interrupted. Because of the short follow-up duration, no repair of tumor cavity was found. However, we still believe that the formation of metastatic tumor cavities is a positive signal for tumor cell necrosis and metastasis control and can be used as a criterion for tumor control instead of relying on the change in tumor volume alone. Moreover, like other targeted antiangiogenesis drugs reported in the previous literature, we also treated Oss with anlotinib as a single agent due to the following reasons: (1) Most patients had received a variety of chemotherapeutics in the past, with relatively poor tumor control effect. In addition, the interference of other drugs in observing the efficacy of anlotinib was excluded. (2) As with any chemotherapeutic agent, we wanted to identify the side effects of anlotinib, because severe side effects may result in patients losing the benefits of anlotinib treatment. (3) Most chemotherapeutic agents are transported through blood vessels to the tumor site to exert antitumor effects, and anlotinib inhibits tumor angiogenesis. In metastasis advanced Oss, it is an effective application of antiangiogenesis targeted drugs like anlotinib is not clearly understood and the effectiveness of anlotinib combination with other chemotherapeutic agents and immunotherapy drugs is unclear.

Regarding the adverse events caused by anlotinib treatment in this study, the most common toxic reactions were hand–foot syndrome, hypertension, diarrhea, fatigue, and pneumothorax. None of these adverse events caused serious consequences in this study. After active symptomatic treatment, these adverse events basically returned to normal. A very small number of patients had to be given a lower dose of anlotinib (reduced the dosage to 10 mg), and one patient stopped anlotinib treatment due to economic reasons. It is worth noting that the incidence of pneumothorax in previous literature on the adverse events of anlotinib was relatively low. However, four patients in our study developed pneumothorax, among which one patient had to have their dosage of anlotinib reduced to 10 mg due to pneumothorax. Symptomatic treatment, including closed thoracic drainage, was provided to this patient outside our hospital. This patient resumed anlotinib treatment after their condition improved. Another patient had to stop taking anlotinib due to pneumothorax. There are many reasons for the occurrence of pneumothorax. For example, Nakamura et al. believed that it may be related to the pleural invasion of lung metastases and tumor necrosis and tumor cavity formation caused by targeted therapy. Previous literature has also shown that anlotinib is mainly used for the treatment of lung cancer and STS. This study observed the efficacy and safety of anlotinib in the treatment of Oss.

Further study by increasing the sample size is necessary to confirm whether the occurrence of pneumothorax may be related to the subtypes of the tumor. In general, this retrospective study found that most adverse events after the treatment were Grade 1–2, and no drug-related deaths occurred, indicating that anlotinib was safe and well tolerated by the patients, except for hand–foot syndrome, diarrhea, and hypertension. Adverse events such as pneumothorax should be discovered and dealt with promptly to improve patient compliance.

This study has some limitations. First, this is an observational and retrospective study without a control group. Data provided by other similar studies can be used to compare the toxicity and effectiveness of anlotinib. Second, before the application of targeted drug therapy, target detection is an important process to obtain better curative effects. However, most patients in our study did not undergo target detection. Third, the number of patients in this study is relatively small. It should be recognized that Oss is a rare malignant tumor. It is not common for patients with Oss that has metastasized after the failure of surgery and chemotherapy to receive anlotinib treatment. To further evaluate the value of anlotinib in the treatment of Oss with metastases, a multicenter, prospective, randomized controlled study is needed.
CONCLUSION

In conclusion, anlotinib was an effective and relatively safe option for patients with metastatic OSS after the failure of standard multimodal therapy. The adverse events were mostly tolerable or relieved after symptomatic treatment. Anlotinib may become a second- or third-line treatment option for advanced OSS. However, its specific clinical application strategies and antitumor mechanisms need to be further explored.

AUTHOR CONTRIBUTIONS

First author; formal analysis; writing—original draft: Hanqing Li. Data curation; investigation: Yang Li. Visualization; software: Qiuchi Ai. Conceptualization; methodology: Lei Song. Writing—reviewing and editing; supervision: Shuai Zhang.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data in the manuscript are authentic and available.

ETHICS STATEMENT

This observational and retrospective study was approved by the Ethics Committee of the Southwest Hospital, the Third Military University.

PATIENT CONSENT STATEMENT

All patients and immediate family members were asked to sign the form of consent for the study.

CONSENT FOR PUBLICATION

Permission has been taken to reproduce materials from other sources.

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