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Secondary pneumothorax as a potential marker of apatinib efficacy in osteosarcoma: a multicenter analysis

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This study was performed to investigate pneumothorax characteristics and association with clinical outcomes in patients with osteosarcoma treated with apatinib. We retrospectively reviewed the medical records of osteosarcoma patients treated with apatinib between January 2016 and April 2020 at three institutions. We evaluated the prevalence, healing time, recurrence, severity, clinical management, and prognosis of pneumothorax in these patients. A total of 54 osteosarcoma patients who received apatinib treatment were enrolled in this study. Among them, 14 patients had pneumothorax. There were significant differences between the patients with and without pneumothorax with regard to the cavitating rate of lung metastases (92.86 vs. 32.50%, respectively, *P*<0.001), objective response rate (42.86 vs. 10.00%, *P*=0.013), disease control rate (85.71 vs. 42.50%, *P*=0.006), 4-month progression-free survival (PFS) rate (57.10 vs. 20.00%, *P*<0.001), and median PFS (5.65 vs. 2.90 months, *P*=0.011). Compared with pneumothorax patients treated with chest tube drainage only [non-staphylococcal enterotoxin C (SEC) group], those treated with chest tube drainage and SEC thoracic perfusion in parallel (SEC group) had a shorter pneumothorax healing time (12.00±4.50 days vs. 24.00±14.63 days for SEC group and non-SEC group, respectively, *P*=0.103), a lower recurrence rate of pneumothorax (25.00% vs. 66.67%, *P*=0.277), and a longer median PFS (5.9 months vs. 4.75 months, *P*=0.964). however, these numerical differences for the SEC/non-SEC data did not reach statistical significance. Pneumothorax and cavitation in lung metastases may be effective prognostic markers for patients with osteosarcoma treated with apatinib. SEC may be effective for treatment of such pneumothorax patients, warranting further study. *Anti-Cancer Drugs* 32: 82–87 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Osteosarcoma is a mesenchymal malignancy with a worldwide incidence of 3.4 per million people per year [1]. Despite the low incidence, there are still more than 4000 new cases diagnosed in China each year. The malignancy shows a predilection for the limbs in adolescent patients. Growth of osteosarcoma at the primary site causes impaired limb function, and metastasis often leads to death; 95% of metastases occur in the lung [2]. Current treatment of osteosarcoma includes surgical resection of all gross disease in conjunction with systemic chemotherapy to control micro-metastatic disease. This treatment yields a 5-year event-free survival rate of approximately 70% for patients with localized osteosarcoma, whereas patients with metastatic or recurrent disease have a poorer prognosis, with a 4-month progression-free survival (PFS) rate of only 12% and overall survival rates lower than 20% [3].

In recent years, with the great success of receptor tyrosine kinase inhibitors (TKIs) in the treatment of malignant tumors, the treatment of osteosarcoma has entered a new era. Sorafenib, apatinib, and regorafenib are TKIs that have been shown to be effective in the treatment of osteosarcoma in clinical trials [4–7]. These TKIs inhibit a variety of tyrosine kinases, and although their multitarget nature has led to effective treatment of osteosarcoma, it has also caused various adverse events. A growing number of studies have shown that pneumothorax is one of adverse events associated with treatment of sarcomas using multitarget TKIs [5,8,9].

As a multitarget TKI marketed for the treatment of advanced or metastatic gastric cancer in China, apatinib has been shown to be effective for the treatment of osteosarcoma. In our previous work, we found that the incidence of pneumothorax in patients with osteosarcoma

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treated with apatinib was 18.18% [10], which was similar to the results of other studies [5,11]. To further investigate this issue, we retrospectively analyzed data for patients with osteosarcoma treated with apatinib at three institutions, focusing on clinical characteristics related to pneumothorax, with the aim of providing more clinical data to support the treatment of osteosarcoma using TKIs.

Material and methods

Study design and eligibility criteria

This study was approved by the Institutional Review Board of the Affiliated Cancer Hospital of Zhengzhou University and performed according to the principles and guidelines of the Declaration of Helsinki. All patients provided written informed consent for data collection and research purposes. This was a multicenter retrospective study of osteosarcoma patients treated at three hospitals: Affiliated Cancer Hospital of Zhengzhou University, First Affiliated Hospital of Zhengzhou University, and Affiliated People's Hospital of Zhengzhou University. We retrospectively reviewed the medical records of osteosarcoma patients treated with apatinib between January 2016 and April 2020.

Inclusion criteria were as follows: (1) histologically proven osteosarcoma; (2) presence of metastatic lung lesions; (3) treatment with apatinib; (4) no history of treatment with other targeted drugs before apatinib treatment; (5) measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and (6) complete clinical data that could be statistically analyzed.

Treatment

Patients received a once-daily oral dose of 500 mg apatinib. This apatinib dose was reduced to 250 mg per day for patients with intolerable adverse events. Apatinib was administered continuously until intolerable adverse events or progressive disease (PD) occurred. Adverse events were assessed using the US National Center Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. If a severe adverse event occurred, apatinib administration was delayed for a maximum of 14 days to enable recovery.

If pneumothorax occurred, patients were treated by chest tube drainage. In the later stage, the patients were treated with staphylococcal enterotoxin C injection (SEC, Xiehe Biology Group, Shenyang, China) thoracic perfusion in parallel. SEC thoracic perfusion was performed as follows: 10 mL SEC, 5 mL 1% lidocaine solution, and 30 mL 0.9% sodium chloride solution were mixed and then injected into the chest cavity via the chest tube. The body position of the patients was changed after injection to make SEC mixture to be evenly distributed throughout the chest. The perfusion was repeated every 3 days for up to five cycles. Removal of the chest tubes was performed based on a strict algorithm and required complete cessation of any air leakage and fluid output <250 mL (clear fluid) per 24 h.

Table 1 Basic characteristics of the two osteosarcoma groups

Characteristics	Patients with pneumothorax (n=14)	Patients without pneumothorax (n=40)	P value
Gender			1
Male	8 (57.14%)	21 (52.50%)	
Female	6 (42.86%)	19 (47.50%)	
Age (years)	22.00±11.70	20.00±9.80	0.564
ECOG PS			0.546
0	7 (50.00%)	24 (60.00%)	
1	7 (50.00%)	16 (40.00%)	
Primary site			0.973
Femur	5 (35.71%)	13 (32.50%)	
Tibia	3 (21.43%)	11 (27.50%)	
Humerus	3 (21.43%)	6 (15.00%)	
Other	1 (7.14%)	4 (10.00%)	
Axial skeleton	1 (7.14%)	3 (7.50%)	
Radial	1 (7.14%)	1 (2.50%)	
Fibula	0 (0.00%)	2 (5.00%)	
Excision of primary lesion			1
No	2 (14.29%)	5 (12.50%)	
Yes	12 (85.71%)	35 (87.50%)	
Metastatic site			0.681
Only lung	11 (78.57%)	34 (85.00%)	
Both bone and lung	3 (21.43%)	6 (15.00%)	
Previous MAP/I chemotherapy			1
No	1 (7.14%)	5 (12.50%)	
Yes	13 (92.86%)	35 (87.50%)	
Time interval (months)	4.36±2.68	4.30±2.41	0.504
Apatinib dosage per administration (mg)	435.46±31.72	428.95±33.87	1

Data are presented as numbers (percentages) or means±SD.
ECOG PS, Eastern Cooperative Oncology Group performance status; MAP/I, high-dose methotrexate, doxorubicin, cisplatin, and/or ifosfamide; Time interval, time interval between the end of chemotherapy and oral apatinib administration.

Table 2 Clinical outcomes of the two osteosarcoma groups

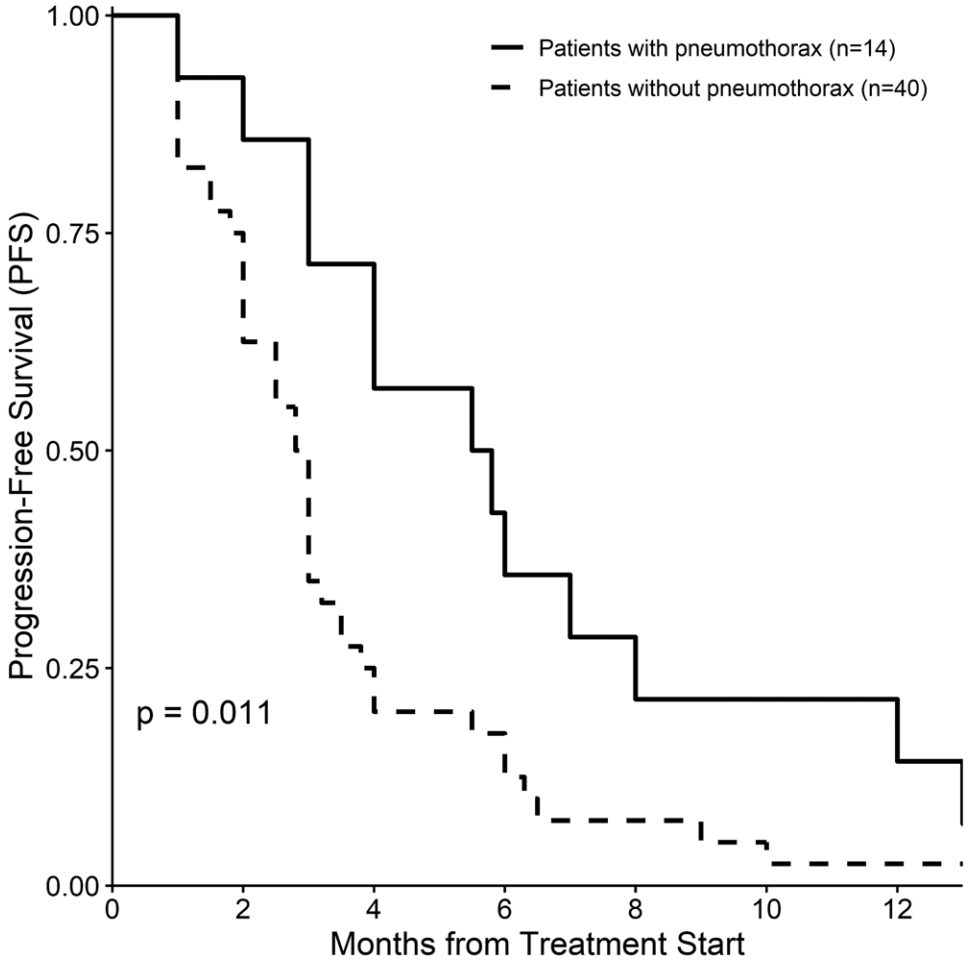
Characteristics	Patients with pneumothorax (n=14)	Patients without pneumothorax (n=40)	P value
Cavitation in lung metastases			<0.001
Yes	13 (92.86%)	13 (32.50%)	
No	1 (7.14%)	27 (67.50%)	
ORR (%)	6 (42.86%)	4 (10.00%)	0.013
DCR (%)	12 (85.71%)	17 (42.50%)	0.006
Median PFS (months)	5.65 (3–8)	2.90 (2–3)	0.011
4-month PFS rate	57.10% (0.284–0.780)	20.00% (0.094–0.335)	<0.001

Data are presented as numbers (percentages), medians (95% confidence interval), or rates (deviations).
DCR, disease control rate; ORR, objective response rate; PFS, progression-free survival.

Evaluation

We reviewed the baseline characteristics of all the osteosarcoma patients enrolled in this study. Specifically, we determined the time interval between the first pneumothorax and apatinib treatment and assessed the prevalence, healing time, recurrence, severity, and clinical management of pneumothorax in these patients. We also evaluated the impact of pneumothorax by comparing the characteristics of the patients with and without pneumothorax. The effectiveness of SEC was evaluated by comparing the characteristics of the patients with pneumothorax treated with and without SEC thoracic perfusion.

Fig. 1



Kaplan–Meier estimates of progression-free survival among osteosarcoma patients with or without pneumothorax.

Statistical analysis

The objective response rate (ORR), disease control rate (DCR), 4-month PFS rate, and cavitating rate of lung metastases during apatinib treatment were evaluated and compared. PFS was estimated by the Kaplan–Meier method and compared using the log-rank test. Group-wise comparison was conducted using Fisher's exact test and the Wilcoxon rank-sum test with continuity correction. Quantitative variables are presented as medians (range) or number of patients (percentage). In all analyses, the *P* values were two-sided, and $P < 0.05$ was considered significant.

The prevalence of pneumothorax was calculated as the percentage of patients suffering from pneumothorax. The healing time for pneumothorax was calculated as the time from chest tube drainage treatment to removal of the chest tubes. The severity of pneumothorax events was graded based on NCI-CTCAE (version 4.0). The objective response and PD were defined based on RECIST (version 1.1). PFS was calculated from the date of initiation of apatinib therapy until radiological progression of disease.

Results

Patient characteristics

A total of 54 osteosarcoma patients who received apatinib treatment were enrolled in this study. Among them, 14 patients had pneumothorax. The characteristics of the patients are shown in Table 1. Comparison of various characteristics revealed no statistically significant difference between the patients with and without pneumothorax (Table 1).

Clinical outcomes

As shown in Table 2, there were significant differences between the patients with and without pneumothorax with regard to the cavitating rate of lung metastases (92.86 vs. 32.50%, respectively, $P < 0.001$), ORR (42.86 vs. 10.00%, $P = 0.013$), DCR (85.71 vs. 42.50%, $P = 0.006$), 4-month PFS rate (57.10 vs. 20.00%, $P < 0.001$; Fig. 1), and median PFS (5.65 vs. 2.90 months, $P = 0.011$; Fig. 1).

Characteristics of pneumothorax

The prevalence of pneumothorax was 25.93%. The time interval between the first pneumothorax and apatinib treatment was 3.3 ± 2.8 months. Among the 14 patients with pneumothorax, 6 patients were treated with chest tube drainage (non-SEC group), and 8 patients were treated with chest tube drainage and SEC thoracic perfusion in parallel (SEC group). As shown in Table 3, compared with the non-SEC group, the SEC group had a shorter pneumothorax healing time (12.00 ± 4.50 days vs. 24.00 ± 14.63 days for SEC group and non-SEC group, respectively), a lower recurrence rate of pneumothorax (25.00 vs. 66.67%), and a longer median PFS (5.9 vs. 4.75 months). Nevertheless, there was no statistically significant difference in these numerical differences and other characteristics between the two groups (Table 3).

Table 3 Basic characteristics of the two pneumothorax groups

Characteristics	SEC group (n=8)	Non-SEC group (n=6)	P value
Gender			1
Male	5 (62.50%)	21 (52.50%)	
Female	3 (37.50%)	19 (47.50%)	
Age	23.62 ± 15.32	20.00 ± 9.80	0.557
ECOG PS			1
0	4 (50.00%)	24 (60.00%)	
1	4 (50.00%)	16 (40.00%)	
Primary site			1
Femur	2 (25.00%)	3 (50.00%)	
Humerus	2 (25.00%)	1 (16.67%)	
Tibia	1 (12.50%)	2 (33.33%)	
Other	1 (12.50%)	0 (0.00%)	
Axial skeleton	1 (7.14%)	0 (0.00%)	
Radial	1 (12.50%)	0 (0.00%)	
Excision of primary lesion			1
No	1 (12.50%)	1 (16.67%)	
Yes	7 (87.50%)	5 (83.33%)	
Metastatic site			0.538
Only lung	7 (87.50%)	4 (66.67%)	
Both bone and lung	1 (12.50%)	2 (33.33%)	
Previous MAP/I chemotherapy			1
No	1 (12.50%)	0 (0.00%)	
Yes	7 (87.50%)	6 (100.00%)	
Pneumothorax grade >2	3 (37.50%)	3 (50.00%)	1
Pneumothorax healing time (days)	12.00 ± 4.50	24.00 ± 14.63	0.103
Recurrence of pneumothorax			0.277
Yes	2 (25.00%)	4 (66.67%)	
No	6 (75.00%)	2 (33.33%)	
Median PFS (months)	5.9 (2-12)	4.75 (1-NA)	0.964

Data are presented as numbers (percentages), means ± standard or medians (95% CI range) deviations.
ECOG PS, Eastern Cooperative Oncology Group performance status; MAP/I, high-dose methotrexate, doxorubicin, cisplatin, and/or ifosfamide; PFS, progression-free survival; SEC, staphylococcal enterotoxin C.

Discussion

To our knowledge, this study is the first to focus on pneumothorax in osteosarcoma patients treated with apatinib. The results of this study showed that the incidence of pneumothorax in osteosarcoma patients treated with apatinib was 25.93%, which was similar to previous reports [5,11]. However, the incidence of pneumothorax in osteosarcoma patients treated with sorafenib and regorafenib, the other two multitarget TKIs that have been shown to be effective in osteosarcoma treatment, was 3 and 0%, respectively [4,6,7]. We speculate that these differences may be attributable to the different targets of these TKIs (Table 4) [12–15]. Nonetheless, the exact reasons for the discrepancy are unknown. Pazopanib is another multitarget TKI that has a high probability of causing pneumothorax in patients with sarcomas [8,16,17]; the targets of pazopanib are also different from those of apatinib (Table 4) [18]. Different targets result in different effectiveness of the two TKIs for osteosarcoma treatment. Based on current evidence, apatinib is more effective than pazopanib for osteosarcoma treatment [5,19]. Although the targets and therapeutic effects of the two drugs are different, the pathological process of pneumothorax caused by the two drugs appears to be the same; this process involves cavitation in lung metastases and finally pneumothorax formation (as shown in Fig. 2) [17,20]. This suggests that both drugs inhibit key targets involved in pneumothorax formation. As shown in Table 4, the shared targets of apatinib and pazopanib include vascular endothelial growth factor receptors (VEGFRs) and stem cell factor receptor (KIT). We performed a literature search and found that bevacizumab and ramucirumab, single-target inhibitors of the VEGFR signaling pathway, can cause pneumothorax [21–23]. However, imatinib, which targets KIT but not VEGFRs (Table 4) [24], has not been reported to cause pneumothorax. This evidence suggests that VEGFRs are involved in pneumothorax development during treatment of sarcomas with TKIs. However, the detailed mechanisms remain unclear and warrant further study.

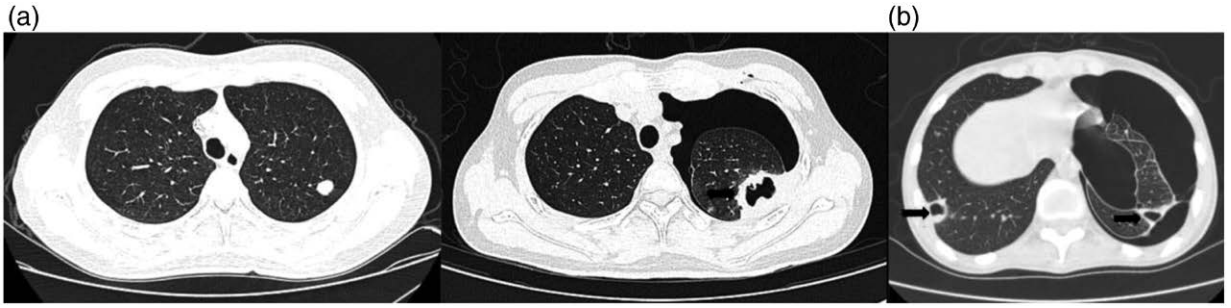
In this study, patients with pneumothorax had a higher cavitating rate in lung metastases than patients without pneumothorax (Table 2, Fig. 2), which was consistent with other reports [8,9]. We speculate that pneumothorax and cavitation in lung metastasis are the result of tumor

Table 4 Targets of apatinib, regorafenib, sorafenib, pazopanib, and imatinib

	Targets (RTKs) and IC_{50} (nM, mean)								
TKI	VEGFR1	VEGFR2	VEGFR3	KIT	RET	PDGFRα	PDGFRβ	FGFR1	Reference
Apatinib	70	1	–	429	13	>1000	–	>10000	12
Regorafenib	13	4.2	46	7	1.5	–	22	202	15
Sorafenib	–	4	20	68	0.4	–	57	580	13
Pazopanib	10	30	47	74	–	71	84	140	18
Imatinib	19500	10700	5700	97	–	72	–	31200	24

IC_{50}, half maximal inhibitory concentration; nM, nmol/L; KIT, stem cell factor receptor; RTKs, receptor tyrosine kinases; TKIs, receptor tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor.

Fig. 2



Typical pathological process of pneumothorax after apatinib treatment in two osteosarcoma patients. Computed tomography scans were obtained at (a1) treatment initiation in case 1, (a2) 6 months after treatment in case 1, and (b) 4 months after treatment in case 2. Arrows indicate cavitation in lung metastases.

necrosis and wound healing disorders caused by apatinib. In other words, pneumothorax and cavitation in lung metastasis are manifestations of the effectiveness of the treatment. This is demonstrated by the prolongation of median PFS in patients with pneumothorax (Table 2, Fig. 1). Interestingly, another study also identified cavitation in lung metastasis as a common effect of apatinib therapy and as a potential prognostic marker for the treatment of gastric and non-small-cell lung cancer patients [25]. And most recently, a study suggests that pneumothorax might be a marker for the favorable clinical outcome following apatinib-treated refractory osteosarcoma [26].

Some of the pneumothorax patients in this study were treated with SEC thoracic perfusion. SEC is the most frequent superantigenic toxin produced by *Staphylococcus aureus*, which was isolated from bovine mastitis [27,28]. SEC can be instilled via an indwelling pleural catheter to induce pleurodesis. SEC is used in pneumothorax treatment because it can cause an inflammatory reaction and adhesion of pleura, leading to resolution of the pneumothorax. SEC is commonly used in the treatment of spontaneous pneumothorax in China [29,30]. To our knowledge, there is no report of SEC for treatment of secondary pneumothorax caused by TKIs. In this study, we found that the healing time was shortened and recurrence rate was reduced in pneumothorax patients treated with SEC. This suggests that SEC may also be effective for treatment of secondary pneumothorax caused by TKIs. For treatment of spontaneous pneumothorax, pleurodesis and thoracoscopic surgery have been widely studied [31–33]; however, we cannot determine whether pleurodesis, including the use of SEC, is superior to thoracoscopic surgery for the treatment of secondary pneumothorax caused by TKIs. The effectiveness of these treatments requires further study.

This study preliminarily evaluated secondary pneumothorax caused by apatinib treatment in osteosarcoma patients with lung metastasis. However, this study had some limitations, including its retrospective design, small sample size, and the absence of a control group. To further investigate secondary pneumothorax caused by TKIs, prospective clinical studies must be performed. The mechanisms underlying this form of pneumothorax also require further study. More importantly, the treatment of secondary pneumothorax, which may involve pleurodesis or thoracoscopic surgery, requires further investigation.

In conclusion, pneumothorax and cavitation in lung metastasis are common adverse events associated with apatinib therapy and may be effective prognostic markers in osteosarcoma patients undergoing apatinib treatment. In addition, SEC may be effective for treatment of pneumothorax in these cases, warranting further study.

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Conflicts of interest

There are no conflicts of interest.

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