CASE REPORT

Pneumothorax as an Adverse Event in Patients with Lung Metastasis of Soft Tissue Sarcoma under Eribulin Treatment

Kohichi Takada¹, Kazuyuki Murase¹, Hajime Nakamura¹, Naotaka Hayasaka¹, Yohei Arihara¹, Satoshi Iyama², Hiroshi Ikeda², Makoto Emori³, Shintaro Sugita⁴, Katsuyuki Nakamura⁵, Koji Miyanishi¹, Masayoshi Kobune² and Junji Kato¹

Abstract:

Pneumothorax has been reported as a pazopanib-associated adverse event in patients with lung metastases of soft tissue sarcoma (STS). However, pneumothorax triggered by eribulin treatment has never been reported. We herein report two cases of spontaneous pneumothorax in patients with STS treated with eribulin. Both patients experienced pneumothorax accompanied by sudden dyspnea on day 9 or 10 of eribulin treatment. These two cases suggest that spontaneous pneumothorax may occur as an adverse event of eribulin treatment in such patients. We should therefore be alert for the potential development of pneumothorax during eribulin treatment of patients with STS and lung metastases.

Key words: eribulin, pneumothorax, soft tissue sarcoma, lung metastases

(Intern Med 58: 3009-3012, 2019)
(DOI: 10.2169/internalmedicine.2790-19)

Introduction

The prognosis for unresectable or metastatic (UM) soft tissue sarcoma (STS) cases remains dismal (1). Standard treatment for most patients with UM-STS is palliative chemotherapy with doxorubicin (Dox) (2). Recently, three new drugs- pazopanib (3), trabectedin (4), and eribulin (5) - have been approved as therapeutic agents for such patients. Notably, eribulin, a novel dynamic microtubule inhibitor, can prolong the overall survival (OS) of patients with UM-STS previously treated with an anthracycline-containing regimen (5).

However, these three drugs show several drug-specific adverse events. Specifically, pneumothorax has emerged as an unexpected life-threatening adverse event of pazopanib in clinical practice since its approval (6, 7). A recent case series found that the incidence of pazopanib-related pneumothorax in patients with lung metastases due to STS is 10.5-14.0%, which was much higher than that noted in phase III data (3, 6, 7). As for eribulin, one of its specific adverse events is peripheral neuropathy because of its pharmacological mechanism (5). Thus far, no cases of eribulin treatment triggering pneumothorax have been reported.

We herein report two cases of spontaneous pneumothorax in patients with STS treated with eribulin.

Case Reports

Patient 1

A 34-year-old man presented with refractory synovial sarcoma and multiple lung, bone and liver metastases. One year earlier, the patient had been diagnosed with synovial
therapy. On the tenth day of eribulin treatment, the patient suddenly felt chest pains and dyspnea. Chest X-ray revealed simultaneous bilateral spontaneous pneumothorax (Fig. 2), which was treated with bilateral drainage of the thoracic cavity. Unfortunately, the patient died two weeks later because of disease progression.

**Patient 2**

A 74-year-old woman was diagnosed with undifferentiated pleomorphic sarcoma (UPS) and relapsed multiple lung metastases. Three years earlier, she had been diagnosed with a left femoral UPS. We initiated neo-adjuvant chemotherapy (NAC) with Dox plus IFM. After three courses of NAC, complete surgical resection was carried out. One year later, chest CT revealed multiple lung metastases. We treated the patient with pazopanib as second-line chemotherapy after three operations for lung metastases. However, five months after the start of pazopanib treatment, CT imaging revealed PD in terms of lung metastases that were close to the pleura (Fig. 3). Subsequently, the patient was treated with eribulin as third-line chemotherapy. On the ninth day of eribulin treatment, the patient developed dyspnea. Right pneumothorax was found by chest X-ray and CT, and cavity formation within lung metastases was not observed (Fig. 4). Pleurodesis with autologous blood was attempted twice to treat the pneumothorax following the insertion of a chest tube and drainage. We performed wedge resection of the right lung by video-assisted thoracoscopic surgery to cure the pneumothorax because pleurodesis was not effective, and the performance status of the patient was good. Pathological analyses revealed the cause of the pneumothorax to be metastasis from the sarcoma. Tumor cells had invaded the thickened pleura (Fig. 5A), with several tumor cells appearing degenerated (Fig. 5B). After she recovered from the pneumothorax, the patient was treated again with eribulin. At the time of writing, the patient’s disease remains stable after four months of eribulin treatment.
Discussion

To our knowledge, this is the first report of pneumothorax related to eribulin treatment in patients with lung metastases from STS. With regard to pazopanib, an accumulated case series supports the conclusion that pazopanib treatment can induce spontaneous pneumothorax in patients with STS (3, 6, 7), with rates of pneumothorax ranging from 2.1% to 14.0%. In addition, Nakano et al. found that risk factors for pneumothorax in patients with STS lung metastases during pazopanib treatment were lung metastases with a ≥30-mm maximum diameter and the presence of a history of pneumothorax before pazopanib treatment (6). In contrast, a recent case control study suggested that pazopanib did not increase the risk of pneumothorax in patients with lung metastases from STS (8). However, that study had several limitations, one being that the odds of developing pneumothorax in patients with STS on pazopanib were retrospectively analyzed using a purposeful selection method. Notably, multivariate analyses identified the presence of a pleural-based mass or a cavity in a metastatic mass as being a risk factor for the development of pneumothorax (8). Accordingly, the established presence of pleural-based metastases may have been related to the development of pneumothorax in both of our cases.

A retrospective study demonstrated that 1.9% of patients with STS and lung metastases developed spontaneous pneumothorax (9). Eribulin has been used for the treatment of patients with UM-breast cancer since 2010 (10); however, the development of eribulin-related pneumothorax in such patients has never been described. Such observations imply that the risk of pneumothorax in patients with lung metastases associated with STS may be due to the intrinsic nature of this cancer. However, whether or not eribulin treatment increases the risk of pneumothorax in patients with lung metastases due to STS remains uncertain. Further investigations will be needed in order to clarify the relationship between eribulin and pneumothorax.

The mechanisms involved in chemotherapy-related pneumothorax have not been fully elucidated; however, several hypotheses have been proposed, including tumor necrosis in-
ducing the formation of a fistula (11). In patient 2, the surgical and pathological findings revealed that metastatic STS cells existed in the portion of the lung that showed an air leak, although the presence of a fistula was unclear. Notably, degenerated tumor cells were observed in the metastatic lesion, which implied that eribulin had been effective. These observations encouraged us to continue eribulin treatment for patient 2 although we speculated that eribulin-induced STS cell death may have led to the development of pneumothorax. In our experience, 2 (16.7%) of 12 patients with lung metastases of STS showed complications with pneumothorax. We were unable to identify any clinical features useful for distinguishing between patients with and without pneumothorax in our small case series. A further investigation with a bigger patient cohort will be needed in order to clarify the mechanisms of eribulin-induced pneumothorax.

Our two cases suggest that spontaneous pneumothorax may occur as an adverse event of eribulin treatment in patients with STS. We should therefore be mindful of the possible development of pneumothorax during eribulin treatment, although the reason for such an association is uncertain at present.

The authors state that they have no Conflict of Interest (COI).

References

1. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 15: 415-423, 2014.
2. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDiS): a randomised controlled phase 3 trial. Lancet Oncol 18: 1397-1410, 2017.
3. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379: 1879-1886, 2012.
4. Kawai A, Araki N, Sugiyama H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol 16: 406-416, 2015.
5. Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 387: 1629-1637, 2016.
6. Nakano K, Mato N, Tomomatsu J, et al. Risk factors for pneumothorax in advanced and/or metastatic soft tissue sarcoma patients during pazopanib treatment: a single-institute analysis. BMC Cancer 16: 750, 2016.
7. Verschoor AJ, Gelderblom H. Pneumothorax as adverse event in patients with lung metastases of soft tissue sarcoma treated with pazopanib: a single reference centre case series. Clin Sarcoma Res 4: 1-4, 2014.
8. Sabath B, Muhammad HA, Balagani A, et al. Secondary spontaneous pneumothorax in patients with sarcoma treated with pazopanib, a case control study. BMC Cancer 18: 937, 2018.
9. Hoag JB, Sherman M, Fasihudin Q, Lund ME. A comprehensive review of spontaneous pneumothorax complicating sarcoma. Chest 138: 510-518, 2010.
10. Cortes J, Vahdat L, Blum JL, et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. J Clin Oncol 28: 3922-3928, 2010.
11. Fiorelli A, Vicidomini G, Napolitano F, Santini M. Spontaneous pneumothorax after chemotherapy for sarcoma with lung metastases: case report and consideration of pathogenesis. J Thorac Dis 3: 138-140, 2011.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).