Ibrutinib Caused Mediastinal Emphysema and Pneumothorax in the Treatment of a Patient with Mantle Cell Lymphoma

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Abstract

A 70-year-old Japanese man with mantle cell lymphoma underwent extensive chemotherapy and radiation because of the relapse of mantle cell lymphoma. He developed mediastinal emphysema and a pneumothorax 14 days after treatment with 560 mg of ibrutinib. The mediastinal emphysema and the right pneumothorax disappeared after the ibrutinib treatment was tapered off. The patient developed interstitial pneumonia without any infection and new lesions of mantle cell lymphoma in the lungs after restarting treatment with 560 mg of ibrutinib. In this case, the patient developed pneumonia after retreatment with ibrutinib, suggesting the small lung fibrosis that penetrated the mediastinum might have caused the emphysema and pneumothorax.

Key Points

The development of mediastinal emphysema and pneumothorax as a result of ibrutinib treatment has not been reported before.

The patient recovered from mediastinal emphysema and a right pneumothorax after tapering off the dosage of ibrutinib.

The complication of emphysema and pneumothorax was consistently observed in a patient receiving ibrutinib who had previously undergone extensive chemotherapy and radiation treatment.

lymphocytic lymphoma, marginal zone lymphoma, and mantle cell lymphoma (MCL) [1, 2]. Here, we report the case of a patient with MCL who developed mediastinal emphysema and a pneumothorax after treatment with ibrutinib.

Case Presentation

The patient was a 70-year-old man who developed MCL in March 2006. The patient was administered two courses of R-CHOP [rituximab 375 mg/m² on day 1, cyclophosphamide 750 mg/m² on day 2, doxorubicin 50 mg/m² on day 2, vincristine 1.5 mg/m² on day 2 (maximum 2 mg/day), and prednisolone 60 mg/day from days 2 to 6], but he developed drug-induced pneumonia. He was treated with prednisolone for the drug-induced pneumonia and recovered. He was then treated with four courses of ESHAP (cisplatin 25 mg/m² on days 1–4, etoposide 40 mg/m² on days 1–4, cytarabine 2000 mg/m² on day 5, and methylate prednisolone 500 mg/day on days 1–5) and went into complete remission in November 2006.

In August 2012, the patient had a recurrence in the stomach. Radiation therapy (36 Gy/24 fr) was performed on the patient's stomach for the MCL. The patient was administered 375 mg/m² of rituximab every 2–3 months. However, the patient developed new lesions of MCL in the scapula in September 2013, and we administered radiation therapy (40 Gy/20 fr) again. After the second complete remission, the patient was administered rituximab on a

Introduction

Ibrutinib is an irreversible small-molecule inhibitor of Bruton's tyrosine kinase with efficacy in B-cell malignancies, including small lymphocytic lymphoma, chronic

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weekly to bi-weekly basis, which was gradually extended to 2–3 months.

In September 2014, we observed a laryngeal tumor. The tumor grew gradually, thus rituximab treatment was administered weekly again in November 2015. By April 2016, the laryngeal tumor was still present, thus the patient was administered eight courses of rituximab and bendamustine (rituximab 375 mg/m² on day 1, bendamustine 90 mg/m² on day 2). The patient went into a third complete remission in January 2017, but developed swelling of the mesenteric lymph nodes.

On 7 September, 2017, the MCL recurred again. The patient was then administered two courses of rituximab and bendamustine (rituximab 375 mg/m² on day 1 and bendamustine 90 mg/m² on days 2–3). The patient also developed gastric cancer complications on 9 September. The patient underwent a distal gastrectomy on 27 October; thus, the treatment of his MCL was interrupted. The MCL progressed and the mesenteric lymph nodes fused to form a bulky abdominal tumor in January 2018. Histopathological diagnosis from a biopsy of the abdominal tumor on 12 January indicated MCL. We administered 560 mg of ibrutinib on 15 January, 2018. Although we observed that the tumor became smaller, the patient reported chest pains on 29 January, 2018. Computed tomography (CT) showed a recurrence of interstitial pneumonia (IP), mediastinal emphysema, and a right pneumothorax (Fig. 1a). Although the abdominal tumor became smaller (though had not disappeared), it was highly likely that mediastinal emphysema and a pneumothorax had occurred with ibrutinib treatment. Therefore, there was a possibility that continuing the treatment with ibrutinib could lead to the recurrence or development of new lesions of mediastinal emphysema and pneumothorax. At the same time, there was also the possibility of aggravation of MCL upon sudden discontinuation of ibrutinib treatment.

Accordingly, we could not continue the treatment with 560 mg of ibrutinib, thus we gradually tapered the dosage off from 19 March. The mediastinal emphysema and right pneumothorax disappeared by 23 April (Fig. 1b). After the

ibrutinib dosage was tapered off, CT images taken on 20 June showed that the abdominal tumor had regrown. The CT images did not show any new lymphoma lesions in the lungs. The patient developed IP on 17 July (Fig. 1c) without any infection (such as a fungus or *Pneumocystis jirovecii*) and new MCL lesions in the lungs after being treated with 560 mg of ibrutinib (restarted from 26 June). The patient died on 23 July because of the progression of MCL.

The mediastinal emphysema and right pneumothorax were new adverse reactions (occurrence of IP is not a new report), and had a score of least 7 on the Naranjo Adverse Drug Reaction Probability Scale [3]. The reactions occurred after ibrutinib administration and improved following the reduction or discontinuation of ibrutinib, they were not caused by MCL or stomach cancer, and did not become more severe even after continuing the administration of other drugs, indicating they are adverse events from ibrutinib treatment.

Discussion

Ibrutinib is sometimes effective with autoimmune diseases [4, 5], inflammation of check-point immunotherapy [6], and graft-vs.-host disease [7, 8]. These reports suggest that ibrutinib modulates B- and T-cell functions and controls immune reactions. However, in vivo, ibrutinib was sometimes reported to lead to the development of IP. Almost all of these patients recovered after the administration of corticosteroids rather than ibrutinib [9–11].

In this case, certain mechanisms were considered as the cause of the mediastinal emphysema and pneumothorax that developed after the patient was treated with ibrutinib. The first was the small lymphoma lesions on the marginal region of the patient's lung. After ibrutinib was administered, the small lymphoma lesions disappeared and the lung tissue did not recover. However, lung lymphoma lesions were not observed in the CT images taken on 17 July, after the uncontrollable progression of the disease. Second, small IP

Fig. 1 **a** Emphysema and pneumothorax observed 14 days after the administration of ibrutinib. **b** Emphysema and pneumothorax disappeared after reducing the dosage of ibrutinib. **c** Interstitial pneumonia developed after restarting the ibrutinib treatment

developed after the first administration of ibrutinib, and IP penetrated the mediastinum to develop mediastinal emphysema and a pneumothorax. In fact, after the ibrutinib treatment was restarted, IP development was observed in the CT images taken on 23 July. These suggested that the small lung fibrosis that penetrated the mediastinum might have caused the emphysema and pneumothorax in this case.

The reasons why IP occurred when we administered ibrutinib are still unclear. Gu et al. reported that ibrutinib treatment leads to the progression of IP in bleomycin-induced pulmonary fibrosis [9]. They showed that ibrutinib treatment increased the apoptosis of epithelial cells and enhanced inflammation and inflammatory cell infiltration in the lungs.

Ibrutinib also increased transforming growth factor-beta expression and myofibroblast generation. In this case, cytokine (transforming growth factor-beta) changes were not measured and bronchoalveolar lavage fluid testing was not performed. We believe this is the first case report of mediastinal emphysema and pneumothorax as a result of ibrutinib treatment. After eliminating various possibilities, we concluded that they are caused by the penetration of small IP.

Conclusion

The details of the mechanism of the emphysema and pneumothorax were unclear. However, the complication of emphysema and pneumothorax was consistently observed in an ibrutinib-treated patient who had previously received extensive chemotherapy and radiation treatment.

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Compliance with Ethical Standards

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Conflict of Interest Yutaka Tsutsumi, Takahiro Sekine, Shinichi Ito, Satomi Matsuoka and Takanori Teshima have no conflicts of interest that are directly relevant to the content of this case report.

Ethics Approval This study was approved by the local Ethics Committee of the Hakodate Municipal Hospital Institutional Review Board.

Consent to Participate Written informed consent was obtained from the patient described in the report. A copy of the consent may be requested from the corresponding author.

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