Thrombocytopenia due to bone marrow metastasis of small cell lung cancer that was stabilized by chemotherapy

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Abstract
Small cell lung cancer (SCLC) is a highly malignant tumor and can metastasize to the bone marrow. Bone marrow metastasis could cause bone marrow dysfunction, such as anemia, leukopenia, and thrombocytopenia. Chemotherapy might aggravate thrombocytopenia, and therefore, it is not certain whether patients with severe thrombocytopenia due to bone marrow metastasis should be treated with chemotherapy. We report the case of a 70-year-old woman with SCLC who developed severe thrombocytopenia (below 20,000/μL) due to bone marrow metastasis. Chemotherapy restored her platelet count to normal levels. Although she discontinued chemotherapy because of higher brain dysfunction that occurred after prophylactic cranial irradiation, thrombocytopenia could be controlled using chemotherapy throughout her clinical course. Chemotherapy may be carried out safely in patients with severe thrombocytopenia due to bone marrow metastasis of SCLC.

Keywords: Small cell lung cancer, bone marrow metastasis, thrombocytopenia

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Introduction
Malignant tumors frequently metastasize to the bone marrow via hematogenous spread. In adults, bone marrow metastasis is most often seen in prostate, breast, and lung cancers, although any tumor can metastasize to the bone marrow¹. However, it is not certain whether chemotherapy can be performed safely in patients with severe thrombocytopenia due to bone marrow metastasis²-⁴.

Small cell lung cancer (SCLC) is a neuroendocrine carcinoma characterized by rapid growth and metastasis. Bone marrow metastasis is found in 15-30% of patients with SCLC, and bone marrow infiltration of SCLC is detected in 35-66% of patients at autopsy⁵. Patients with bone marrow metastasis of SCLC, which might cause anemia, leukopenia, and thrombocytopenia, have a significantly worse prognosis⁶. SCLC is highly sensitive to chemotherapy, and it is possible that patients with bone marrow metastasis of SCLC are treatable with chemotherapy, even if thrombocytopenia is observed⁷-⁸.

We were able to safely treat a patient with severe thrombocytopenia due to bone marrow metastasis of SCLC with chemotherapy. Her platelet count could be stabilized by chemotherapy, although she and her family eventually chose to discontinue chemotherapy because she suffered higher brain dysfunction after brain irradiation. Informed consent was obtained from the family of the patient.

Case
A 70-year-old woman presented with a dry cough. She initially visited another hospital, and computed tomography (CT) of the chest revealed subcarinal lymph node swelling and consolidation in the lingular segment of the left lung. She was referred to our hospital, and we performed bronchoscopy and diagnosed the tumor as SCLC. The clinical staging was cT3N2M0 (stageIII A). She was treated with four cycles of cisplatin (80 mg/m², day 1) and etoposide (100 mg/m², days 1, 2 and 3). Concurrent with chemotherapy, radiation therapy was administered twice daily, with a total dose of thoracic radiation therapy of 45 Gy. After chemoradiotherapy, chest CT indicated that she was in complete remission from lung cancer. Prophylactic cranial irradiation of 25 Gy in 10 fractions was performed.

Approximately 6 months after chemoradiotherapy, radiation pneumonitis developed in the left lung, which corresponded to the radiation area. Oral prednisolone
was administered. One month after administration of prednisolone, outpatient laboratory testing revealed a decrease in the platelet count, from 212,000/μL to 79,000/μL. Initially, drug-induced thrombocytopenia was suspected, so sulfamethoxazole-trimethoprim and proton pump inhibitor were discontinued. However, her platelet count dropped to 17,000/μL within 2 weeks. She was then admitted to our hospital.

She was afebrile (36.0°C), with blood pressure of 110/68 mmHg and a pulse rate of 71 beats/min, which were within the normal range. The bilateral cervical lymph node and right supraclavicular lymph node were swollen. Heart and lung auscultation were normal. The abdominal wall was soft and nontender without organomegaly. There was no petechiae or rash. Blood laboratory test revealed severe thrombocytopenia; the white blood cell count was 4,950/μL, the hemoglobin was 13.9 g/dL, and the platelet count was 17,000/μL. The prothrombin time international normalized ratio was 0.94, the activated partial thrombin time was 28.2 sec, the fibrinogen level was 308 mg/dL, and the fibrin degradation product was 15.1 μg/mL. Pro-gastrin-releasing peptide (ProGRP) and neuron specific enolase (NSE), specific tumor markers for SCLC, were both elevated; the ProGRP level was 1239.8 pg/mL and the NSE level was 397 ng/mL. The lymphedema and elevation of tumor markers indicated recurrence of SCLC. A bone marrow biopsy was performed for evaluation of thrombocytopenia. Examination of the bone marrow showed decreased megakaryocyte number and emergence of small lung cancer cells, which accounted for 59.6% of the total cells (Fig. 1). The thrombocytopenia was determined to be the result of bone marrow metastasis of SCLC. Chest CT scan revealed enlargement of the right supraclavicular lymph node (40 mm × 30 mm) and the right superior mediastinal lymph node (23 mm × 21 mm).

The patient complained of low back pain, and lumbar magnetic resonance imaging (MRI) showed multiple metastases in the lumbar body (Fig. 2).

Platelet transfusion was performed every 2-3 days.
to maintain a platelet count above 10,000/μL. Before chemotherapy, platelet transfusion was performed for two successive days to elevate the platelet count above 50,000/μL. She was treated with four cycles of carboplatin (CBDCA) (AUC 4, Day1) and etoposide (ETP) (80 mg/m², days 1, 2, and 3). After initiation of chemotherapy, the platelet count recovered to more than 100,000/μL without platelet transfusion (Fig 3). Approximately 2 months after the last administration of CBDCA and ETP, chest CT showed that the right supraclavicular lymph node (17 mm × 16 mm) and the right superior mediastinal lymph node (12 mm × 11 mm) had shrunk significantly,
and there were no new lesions. However, soon after the chest CT, the platelet count dropped again, to 48,000/μL, and tumor markers increased. Pain in the vertebral body metastases had worsened, and lumbar MRI showed development of multiple metastases in the lumbar body. After platelet transfusion, she was treated with amrubicin (AMR) (35 mg/m², days 1, 2 and 3) as 3rd-line chemotherapy. Her platelet count recovered to 115,000/μL after one cycle of AMR (Fig 3). However, she and her family did not want to continue chemotherapy, because higher brain dysfunction had developed after cerebral radiation therapy. Approximately 2 months after discontinuation of chemotherapy, she died.

**Discussion**

Bone marrow metastasis is observed in all solid tumors, and most frequently in prostate cancer, breast cancer, lung cancer, and neuroblastoma. Bone marrow metastasis does not always cause pancytopenia. Bone marrow metastasis has been reported to cause anemia in 66.6% of cases, thrombocytopenia in 83.3%, and leukopenia in 50%[1]; however, another report observed thrombocytopenia in only 33.3% of patients with bone marrow metastasis[2]. SCLC is highly malignant and known to metastasize to the bone marrow. Che et al. reported that, among 26 patients, 10 patients presented with thrombocytopenia, with platelet counts less than 75,000/μL. The median survival time of these patients was only 4.29 months. Twenty of 26 patients with bone marrow metastasis were treated with chemotherapy, and they had a longer survival time than the 6 patients who were not treated with chemotherapy[3]. Nevertheless, it is still uncertain whether patients with severe thrombocytopenia due to bone marrow metastasis should be treated with chemotherapy. Chemotherapy is expected to reduce cancer cells in the bone marrow and consequently increase thrombocytes, although chemotherapy itself might induce thrombocytopenia. Asai et al. reported complete remission in a SCLC patient with thrombocytopenia due to bone metastasis treated with AMR[4].

There is not enough evidence that prophylactic platelet transfusion is superior to therapeutic platelet transfusion after minor bleeding. Prophylactic platelet transfusion is usually performed to avoid fatal bleeding when severe thrombocytopenia is observed during chemotherapy. There is no difference in the risk of severe or life-threatening bleeding between standard trigger (10,000/μL) and higher trigger (20,000 or 30,000/μL) transfusion, but the frequency of the platelet transfusion is higher in the higher trigger group than in the standard trigger group. Therefore, transfusion is usually considered when the platelet count drops, or is expected to drop below 10,000/μL[5]. In this case, the decrease in platelet count was so rapid that platelet transfusion was performed every 2-3 days in order to keep her platelet count above 10,000/μL. Four cycles of chemotherapy were able to be carried out without the need for platelet transfusion, and her platelet count recovered to more than 100,000/μL. However, her lung cancer recurred after a short interval. After one cycle of 3rd-line AMR, her platelet count was elevated to above 100,000/μL. Her platelet count could be maintained above 10,000/μL with chemotherapy throughout her clinical course.

In conclusion, SCLC is prone to metastasize to the bone marrow, which can cause thrombocytopenia. Although it is not certain whether patients with severe thrombocytopenia should be treated with chemotherapy, our patient who suffered severe thrombocytopenia was able to be treated with chemotherapy safely. She survived for approximately 6 months after diagnosis of bone marrow metastasis.

**References**

1) Kaur, G., Basu, S., Kaur, P., & Sood, T. (2011) Metastatic Bone Marrow Tumors: Study of Nine Cases and Review of the Literature. J. Blood. Disord. Transfus. 110: 02.

2) Pahouja, G., Wesołowski, R., Reinbold, R., Tozbikian, G., Berger, M., Mangini, N., and Lasuberg, M. B. (2015) Stabilization of bone marrow infiltration by metastatic breast cancer with continuous doxorubicin. Cancer. Treat. Commun. 3: 28-32.

3) Takeyama, H., Sakiyama, T., Wakasa, T., Kitani, K., Inoue, K., Kato, H., Ueda, S., Tsujie, M., Fujiwara, Y., Yukawa, M. and Ohta, Y. (2017) Disseminated carcinomatosis of the bone marrow with disseminated intravascular coagulation as the first symptom of recurrent rectal cancer successfully treated with chemotherapy: A case report and review of the literature. Oncol. Lett. 13: 4290-4294.

4) Lim, D.H., Lee, S.I. and Park, K.W. (2014) Bone marrow metastasis of colon cancer as the first site of recurrence: A case report. Oncol. Lett. 8: 2672-2674.

5) Trillet, V., Revel, D., Combaret, V., Favrot, M., Loire, R., Tabib, A., Pages, J., Jacquetem, P., Bomsart, A. and Mornex, J.F. (1989) Bone marrow metastases in small cell lung cancer: detection with magnetic resonance imaging and monoclonal antibodies. Br. J. Cancer. 60: 83-88.

6) Zych, J., Polowicz, Z., Wiatr, E., Broniek, A., and Rowinska-Zakrzewska, E. (1993) The prognostic significance of bone marrow metastases in small cell lung cancer patients. Lung Cancer. 10: 239-245.

7) Che, Y., Luo, Y., Wang, D., Shen, D. and Yang, L. (2018) Clinical Analysis of Small Cell Lung Cancer with Bone Marrow Metastases. Zhongguo Fei Ai Za Zhi 21: 403-407.

8) Asai, N., Ohkuni, Y., Matsuda, M., Narita, M. and Kaneko, N. (2013) Incremental low doses of amrubicin for the treatment of bone marrow metastasis in small cell lung cancer. Jornal brasileiro de pneumologia: publicacao oficial da Sociedade Brasileira de Pneumologia e Tisiologia 39: 108-110.

9) Sar, R., Aydogdu, I., Ozan, S., Sevinc, A. and Buyukberber, S. (2001) Metastatic bone marrow tumours: a report of six cases and review of the literature. Haematologia 31: 215-223.

10) Estcourt, L.J., Stanworth, S.J., Doree, C., Hopewell, S., Trivella, M. and Murphy, M.F. (2015) Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst. Rev. 11: CD010983.

Thrombocytopenia due to bone marrow metastasis