Successful treatment of pyrotinib for bone marrow metastasis induced pancytopenia in a patient with non-small-cell lung cancer and ERBB2 mutation

Yanyan Wu1†, Jun Ni1†, Xiaoyan Chang2, Xiaotong Zhang1 & Li Zhang1

1 Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
2 Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Keywords
Bone marrow metastasis; ERBB2 mutation; NSCLC; pyrotinib.

Introduction
Human epidermal growth factor receptor 2 mutations (HER2, ERBB2) have been found in about 2% of patients with non-small cell lung cancer (NSCLC) 1,2. However, in the past 10 years, effective targeted therapies have not been identified. Recently, Wang et al. 3 reported that pyrotinib, an irreversible pan ErbB inhibitor, provided an overall response rate of 53.5% in a phase 2 study. Bone marrow metastasis is rare in patients with lung adenocarcinoma, and has been reported to be associated with poor prognosis. Here, we present a rare NSCLC case with bone marrow metastasis carrying ERBB2 mutations which responded well to pyrotinib therapy.

Case presentation
A 62-year-old woman (non-smoker) was diagnosed with stage IIIb NSCLC in May 2018. Lung histopathology confirmed adenocarcinoma (Fig 1a). Next-generation sequencing (NGS) showed an ERBB2 exon 20 insertion mutation (p.E770delinsEAYVM 24.34%) and a TP53 mutation (p.S241F 10.98%), with a PD-L1 tumor proportion score less than 1%. The patient received six cycles of chemotherapy (pemetrexed/cisplatin) combined with pembrolizumab, underwent radiotherapy of the right lung lesion (64 Gy/eight fractions, three fractions a week) and received six cycles of pemetrexed afterwards as maintenance therapy. Clinical response was evaluated every two cycles as stable disease. However, after six cycles of maintenance...
therapy, multiple bone metastatic lesions were detected on bone scan in June 2019 (Fig 2). The patient refused further chemotherapy and received one cycle of anlotinib (a multitargeting tyrosine kinase inhibitor and angiogenesis inhibitor) without any improvement. On 6 August 2019, she was unconscious and was admitted to hospital. Blood tests showed anemia, thrombocytopenia, hypercalcemia, and elevation of creatinine. Coagulation profile suggested disseminated intravascular coagulation (DIC). Several serum tumor markers were significantly elevated (Table 1).

Hepatic metastases was confirmed by computed tomography (CT) scan (Fig 3a–c). Bone marrow biopsy suggested bone marrow metastasis (Fig 1b,c). The NGS of bone marrow biopsy revealed the copy number alteration of ERBB2 gene ($n = 3.34$) and an ERBB2 exon 20 insertion mutation as previously described (p.Y772_A775dupYVMA 38.45%).

On 18 August 2019, pyrotinib therapy (240 mg q.d.) was initiated, based on ERBB2 exon 20 insertion mutation. One month later, platelet count, renal function and coagulation function of the patient had returned to normal and

---

Figure 1 Lung and bone marrow biopsy pathology of the patient. (a) Lung biopsy pathology at diagnosis, May 2018; (b) bone marrow biopsy pathology in August 2019, metastatic adenocarcinoma was seen in the bone marrow of the patient. Metastatic adenocarcinoma cells are indicated with an arrow; and (c) immunohistochemical result showed that metastatic adenocarcinoma cells in bone marrow were positive for TTF-1.

Figure 2 Bone scan of the patient. Increased uptake was detected in multiple ribs, spines, pelvic bones and bilateral sacroiliac joints.
Table 1  Laboratory data of the patient

| Blood tests                       | Reference range, adult female | 6 August On admission | 18 August Before pyrotinib therapy | 23 August Five days after pyrotinib therapy | 17 September One month after pyrotinib therapy | 16 October Two months after pyrotinib therapy |
|-----------------------------------|-------------------------------|-----------------------|-----------------------------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Complete blood count              |                               |                       |                                   |                                             |                                               |                                               |
| WBC count, \( \times 10^9/L \)    | 3.5–9.5                       | 11.4                  | 8.3                               | 5.6                                         | 4.4                                           | 4.3                                           |
| NEUT count, \( \times 10^9/L \)   | 2.0–7.5                       | 7.9                   | 7.4                               | 3.7                                         | 2.7                                           | 2.8                                           |
| HGB, g/L                          | 110–150                       | 100                   | 71                                | 74                                          | 72                                            | 92                                            |
| PLT count, \( \times 10^9/L \)    | 100–300                       | 31                    | 22                                | 48                                          | 220                                           | 268                                           |
| Electrolytes                      |                               |                       |                                   |                                             |                                               |                                               |
| Sodium, mmol/L                    | 135–145                       | 160                   | 136                               | 136                                         | 137                                           | 138                                           |
| Potassium, mmol/L                 | 3.5–5.5                       | 3.7                   | 3.6                               | 4.2                                         | 4.0                                           | 5.0                                           |
| Chloride, mmol/L                  | 96–111                        | 113                   | 97                                | 102                                         | 102                                           | 103                                           |
| Calcium, mmol/L                   | 2.13–2.70                     | 4.61                  | 3.19                               | 2.09                                         | 2.09                                          | 2.19                                          |
| Creatinine, umol/L                | 45–84                         | 267                   | 141                               | 80                                          | 62                                            | 56                                            |
| Coagulation function              |                               |                       |                                   |                                             |                                               |                                               |
| PT, s                             | 10.4–12.6                     | 13.9                  | 13.3                               | 12.3                                        | 12.5                                          | –                                             |
| APTT, s                           | 23.3–32.5                     | 34.7                  | 29.8                               | 29.4                                        | 25.4                                          | –                                             |
| Fbg, g/L                          | 1.8–3.5                       | 1.4                   | 1.9                                | 2.8                                         | 4.0                                           | –                                             |
| D-Dimer, mg/L FEU                 | 0–0.55                        | 19.62                 | 40.41                              | 24.67                                       | 4.25                                          | –                                             |
| FDP, umol/L                       | 0–5.0                         | 28.96                 | 217.3                              | 76.6                                        | 10.7                                          | –                                             |
| Serum tumor markers               |                               |                       |                                   |                                             |                                               |                                               |
| CA19-9, U/mL                      | 0–34.0                        | 57.3                  | –                                 | 103.9                                       | 62.9                                          | 65.3                                          |
| CEA, U/mL                         | 0–5.0                         | 5851.0                | –                                 | 4455.0                                       | 5413.0                                        | 382.30                                        |
| CA125, U/mL                       | 0–35.0                        | 629.0                 | –                                 | 594.3                                       | 261.2                                         | 408.6                                         |
| CYFRA                             | 0–3.5                         | –                     | –                                 | 14.9                                        | 4.9                                           | 8.3                                           |
| 21-1, U/mL                        |                               |                       |                                   |                                             |                                               |                                               |
| CA242, U/mL                       | 0–20.0                        | 65.6                  | –                                 | 56.0                                        | 47.8                                          | 47.7                                          |
| NSE, U/mL                         | 0–16.3                        | 99.4                  | –                                 | 24.7                                        | 13.9                                          | 25.0                                          |
| CA72-4, U/mL                      | 0–9.8                         | 290.2                 | –                                 | 353.2                                       | 12.9                                          | 14.6                                          |
| CA15-3, U/mL                      | 0–25.0                        | 35.4                  | –                                 | 45.6                                        | 29.3                                          | 24.6                                          |
| SCCAg, U/mL                       | 0–2.7                         | 1.6                   | –                                 | 1.1                                         | 0.8                                           | 1.0                                           |
| proGRP, U/mL                      | 0–69.2                        | 259                   | –                                 | 211                                         | 250                                           | 148                                           |

APTT, activated partial thromboplastin time; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragments; Fbg, fibrinogen; FDP, fibrinogen degradation product; HGB, hemoglobin; NEUT, neutrophil; NSE, neuron-specific enolase; PLT, platelet; proGRP, gastrin-releasing peptide precursor; PT, prothrombin time; SCCAg, squamous cell carcinoma antigen; WBC, white blood cells.
Pyrotinib dose was subsequently increased to 320 mg q.d. Two months later on 16 October 2019, she was assessed as stable disease (Table 1, Fig 3d-f).

**Discussion**

With the discovery of driver mutations such as epidermal growth factor receptor (EGFR) and the development of tyrosine kinase inhibitor (TKI) therapies targeting these mutations, the treatment of NSCLC has moved from conventional chemotherapy to targeted therapies. Human epidermal growth factor receptor 2 mutations (HER2, ERBB2) are found in about 2% of NSCLC, with a predominance in women and non-smokers. About 96% of ERBB2 mutations are exon 20 insertions, and 83% of those are a recurrent 12 base-pair insertion causing duplication of amino acids YVMA at codon 775. Patients with ERBB2 mutations have previously shown a low response to pemetrexed-based first-line chemotherapy. Immunotherapy achieved limited efficacy in these patients with response rates varying from 7% to 27%. Since 2006, several case reports and case series have suggested trastuzumab, afatinib, dacomitinib and neratinib as potential targeted therapies for patients with NSCLC carrying ERBB2 mutations. Early clinical activity has also been seen with the dual EGFR TKIs, poziotinib and TAK-788. Mazières et al. have recently reported 65 patients receiving ERBB2-targeted therapies (trastuzumab and afatinib) with an overall response rate (ORR) of 50.9% and a median PFS of 4.8 months. In 2018, Wang et al. reported pyrotinib, as a pan HER receptor tyrosine kinase inhibitor, showed superior anti-tumor effect than afatinib and trastuzumab in vitro. In a phase 2 study of 15 patients, treatment with pyrotinib provided an ORR of 53.5% and a median PFS of 6.4 months. In our case, the patient carried an exon 20 insertion leading to duplication of amino acid YVMA at codon 775 in ERBB2, which is the most often seen mutation in NSCLC. She was given pyrotinib 240 mg q.d. first for renal insufficiency, and the dose was adjusted to 320 mg q.d. The patient achieved stable disease and recovered from acute kidney injury and bone marrow depression, which is in accordance with the report by Wang et al.

Bone marrow metastasis is rarely reported in NSCLC. Tumor cells invading bone marrow will lead to pancytopenia and hematological disorders such as DIC and microangiopathic hemolytic anemia. In our case, it is first reported that the NGS of bone marrow confirmed homeo-tic mutations with lung tissue and the patient recovered from severe anemia, thrombocytopenia and DIC after pyrotinib therapy.

**Disclosure**

The authors declare there are no conflicts of interest.
References

1 Mazieres J, Peters S, Lepage B et al. Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* 2013; 31 (16): 1997–2003.

2 Arcila ME, Chaft JE, Nafa K et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. *Clin Cancer Res* 2012; 18 (18): 4910–8.

3 Wang Y, Jiang T, Qin Z et al. HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. *Ann Oncol* 2019; 30 (3): 447–55.

4 Buttitta F, Barassi F, Fresu G et al. Mutational analysis of the HER2 gene in lung tumors from Caucasian patients: Mutations are mainly present in adenocarcinomas with bronchioloalveolar features. *Int J Cancer* 2006; 119 (11): 2586–91.

5 Tomizawa K, Suda K, Onozato R et al. Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. *Lung Cancer* 2011; 74 (1): 139–44.

6 Robichaux JP, Elamin YY, Vijayan RSK et al. Pan-cancer landscape and analysis of ERBB2 mutations identifies Poziotinib as a clinically active inhibitor and enhancer of T-DM1 activity. *Cancer Cell* 2019; 36 (4): 444–57.

7 Wang Y, Zhang S, Wu F et al. Outcomes of Pemetrexed-based chemotherapies in HER2-mutant lung cancers. *BMC Cancer* 2018; 18 (1): 326.

8 Guisier F, Dubos-Arvis C, Viñas F et al. Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol* 2020; 15 (4): 628–36.

9 Mazieres J, Drilon A, Lasique A et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry. *Ann Oncol* 2019; 30 (8): 1321–8.

10 De Greve J, Teugels E, Geers C et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer* 2012; 76 (1): 123–7.

11 Kris MG, Camidge DR, Giaccone G et al. Targeting HER2 aberrations as actionable drivers in lung cancers: Phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann Oncol* 2015; 26 (7): 1421–7.

12 Gandhi L, Bahleda R, Tolaney SM et al. Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. *J Clin Oncol* 2014; 32 (2): 68–75.

13 Hyman DM, Piha-Paul SA, Won H et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature* 2018; 554 (7691): 189–94.

14 Masood A, Kancha RK, Subramanian J. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer harboring uncommon EGFR mutations: Focus on afatinib. *Semin Oncol* 2019; 46 (3): 271–83.

15 Mazieres J, Barlesi F, Filleron T et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: Results from the European EUHER2 cohort. *Ann Oncol* 2016; 27 (2): 281–6.