CASE REPORT

Erlotinib-Induced Cardiomyopathy in a Patient with Metastatic Non-Small Cell Lung Cancer

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Summary

Erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, is a targeted drug used for the treatment of non-small cell lung cancer (NSCLC). Erlotinib is considered relatively safe and generally well-tolerated, with rarely reported cardiac side effects. Herein, we report a case of cardiomyopathy that developed during erlotinib treatment for NSCLC. Two months after erlotinib initiation, our 70-year-old female patient complained of progressive dyspnea, and a diagnostic endomyocardial biopsy confirmed non-specific cardiomyopathy, indicating erlotinib-induced cardiomyopathy. We believed that continued administration of erlotinib would exacerbate her heart failure, while treatment of the heart failure with intensive monitoring would allow the administration of erlotinib to be continued. This case report highlights the potential cardiotoxic effects of erlotinib and suggests the need for close clinical and echocardiographic follow-up of patients receiving erlotinib.

Key words: Cardio-oncology, Onco-cardiology, CTRCD, Heart failure, EGFR-TKI

Erlotinib is a first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and based on its proven effectiveness in clinical trials, erlotinib is the first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) harboring the EGFR mutation. This agent is generally well-tolerated, and the incidence of adverse cardiovascular events is very low. However, physicians should remain alert to the potential for cardiovascular toxicity resulting from erlotinib treatment. Herein, we present a case of erlotinib-induced cardiomyopathy in a patient with advanced NSCLC.

Case Report

In April 2018, a 70-year-old woman with diabetes, dyslipidemia, and hypertension was diagnosed with metastatic lung adenocarcinoma harboring an EGFR deletion mutation in exon 19. She was initially treated with gefitinib (250 mg orally once daily). However, due to the development of stomatitis and hepatic injury, her treatment was switched to erlotinib (50 mg once daily orally) in June 2018. The erlotinib dose was then up-titrated to 100 mg and maintained. In August 2018, after taking erlotinib for 2 months, the patient complained of rapidly worsening dyspnea over the previous 7 days and was hospitalized at our institution.

Laboratory investigations on admission showed an increased N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration of 8127 pg/mL without elevated troponin levels (Table). Chest radiography revealed enlargement of the cardiac silhouette with pulmonary edema and pleural effusion (Figure 1A). An electrocardiogram revealed newly appeared T-wave inversions in the V5 and V6 leads (Figure 1B). On echocardiography, the left ventricular ejection fraction (LVEF) was significantly decreased compared to that before erlotinib treatment (35% versus 67%) (Figure 2). Transmitral flow (TMF) before the administration of erlotinib showed an impaired relaxation pattern, but the TMF on admission was monomodal due to tachycardia, and was difficult to evaluate (Figure 2). The echocardiographic findings, along with an increase in tricuspid regurgitation velocity and E/e’, suggested an increase in left atrial pressure (Figure 2). Cardiac magnetic resonance imaging revealed severely impaired global systolic function (LVEF 34%) with extensive mid-myocardial late gadolinium enhancement throughout the LV. T2-weighted short-tau inversion recovery images did not show evidence of myocardial edema. The patient underwent coronary angiography, which excluded relevant coronary diseases (0% stenosis in all of the 15 coronary artery segments). Confronted with unclear acute heart failure, an endomyocardial biopsy was performed. Histopathological analysis of the biopsy samples taken from the right ventricular septum revealed myocyte disarray with nuclear pleomorphism and mild fibrosis within the myocardium (Figure 3). No inflammatory cell infiltration, amyloid deposits, or necrosis were observed. She was treated with carperitide, enalapril, spironolactone, carvedilol, and furosemide (Figure 4), and her cardiac condition
Figure 1. Chest radiograph and electrocardiogram findings. A: The left panel shows a chest radiograph obtained before starting erlotinib treatment. The middle panel shows a chest radiograph on admission for acute heart failure, revealing cardiomegaly with pulmonary edema and pleural effusion. The right panel shows a chest radiograph at discharge. B: Electrocardiogram recording before erlotinib (left), admission (middle), and discharge (right). The red arrows indicate T-wave inversions.

Table. Clinical Presentation and Hematological Parameters

|                      | Before erlotinib | On admission | At discharge | At the end of follow-up |
|----------------------|------------------|--------------|--------------|-------------------------|
| SpO₂ (%)             | 98               | 92           | 98           | 98                      |
| O₂ (L)               | 0                | 2            | 0            | 0                       |
| AST (U/L)            | 30               | 16           | 20           | 15                      |
| ALT (U/L)            | 72               | 7            | 6            | 4                       |
| LD (U/L)             | 193              | 209          | 168          | 171                     |
| Na (mEq/L)           | 134              | 138          | 141          | 137                     |
| K (mEq/L)            | 3.8              | 3.7          | 3.6          | 4.7                     |
| CRE (mg/dL)          | 0.85             | 0.68         | 0.80         | 1.74                    |
| BUN (mg/dL)          | 10.9             | 13.2         | 15.7         | 33.7                    |
| eGFR                 | 50.6             | 64.6         | 54.1         | 23.0                    |
| Hb (g/dL)            | 8.7              | 11.5         | 10.4         | 10.4                    |
| WBC (10⁹/μL)         | 7500             | 6000         | 5400         | 7200                    |
| PLT (10⁴/μL)         | 16.6             | 17.9         | 19.7         | 9.1                     |
| CRP (mg/dL)          | 1.96             | 0.47         | 0.83         | 0.04                    |
| NT-proBNP (pg/dL)    | N/A              | 8127         | N/A          | N/A                     |
| BNP (pg/dL)          | N/A              | N/A          | 588          | 159                     |

NA indicates not assessed.
**Figure 2.** Echocardiogram findings. The panels show the transmitral flow velocity at each time point. DT indicates deceleration time; HR, heart rate; IVC, inferior vena cava; LAVI, left atrial volume index; LVDD, left ventricular dimension in diastole; LVDS, left ventricular dimension in systole; LVEF, left ventricular ejection fraction; and TRV, tricuspid regurgitation velocity. For the E/e’ calculation, the average e’ velocity obtained from the septal and lateral sides of the mitral annulus was used.

| Metric                      | Before erlotinib | On admission | At discharge | At the end of follow-up |
|-----------------------------|------------------|--------------|--------------|-------------------------|
| HR, bpm                     | 86               | 104          | 80           | 80                      |
| LVDD, mm                    | 36.8             | 50.5         | 52.7         | 44.5                    |
| LVDS, mm                    | 23.3             | 41.7         | 39.3         | 32.1                    |
| LVEF, %                     | 67               | 35           | 48           | 50                      |
| LAVI, mL/m²                 | 20               | 37           | 36           | 22                      |
| E, cm/s                     | 87               | NA           | 87           | 47                      |
| A, cm/s                     | 101              | NA           | 120          | 86                      |
| DT, ms                      | 216              | NA           | 171          | 225                     |
| E/A                         | 0.86             | NA           | 0.73         | 0.55                    |
| Lateral e’, cm/s            | 5.6              | 3.5          | 3.6          | 4.4                     |
| Septal e’, cm/s             | 8.1              | 2.5          | 3.0          | 3.4                     |
| E/e’                        | 12.7             | NA           | 26.4         | 12.1                    |
| TRV, m/s                    | 2.78             | 2.91         | 2.37         | 2.35                    |
| IVC, mm                     | 21               | 16           | 13           | 5                       |

**Figure 3.** Histological analysis of endomyocardial biopsy. Hematoxylin and eosin (H&E, left) and Masson’s trichrome (right) staining of myocardial biopsy samples. Histopathological analysis revealed myocyte disarray with nuclear pleomorphism and mild fibrosis within the myocardium.

Improved after 1 week.

The patient’s heart failure was relatively mild, with stable hemodynamics; therefore, it was thought that cancer, not heart failure, would determine her prognosis. The 1-year survival rate for the patient was estimated to be approximately 30%. However, at this time, her cancer was controlled by erlotinib. Although the discontinuation of erlotinib and change to other anticancer drugs were considered, we decided to continue erlotinib with closely monitored treatment for heart failure because discontinuation of the drug would have led to cancer progression. The patient was able to continue erlotinib treatment for 9 months without acute exacerbation of chronic heart failure, but due to cancer progression, her anticancer drug was
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Figure 4. Clinical course. Orange dots represent LV EF, blue dots represent NT-proBNP, and blue triangles indicate BNP levels. LV EF indicates left ventricular ejection fraction; BNP, brain natriuretic peptide; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

switched to osimertinib (Figure 4). Treatment for heart failure continued thereafter, and cardiac function was maintained until the end of the follow-up period (12 months after starting erlotinib) (Figure 4).

Discussion

To date, only 4 cases of cardiovascular adverse events (3 myocardial infarctions and one dilated cardiomyopathy) have been reported as side effects of erlotinib.4-6) Kus, et al.4) reported two cases of ST-segment elevation myocardial infarction during erlotinib treatment for NSCLC. Ding, et al.5) also reported a similar case of myocardial infarction following erlotinib treatment. Pinquie, et al.6) reported dilated cardiomyopathy in a patient with NSCLC who was administered maintenance erlotinib for 26 months after 6 courses of cisplatin/pemetrexed treatment. Our case presented with heart failure without coronary artery lesions and was similar to the last mentioned case of dilated cardiomyopathy rather than the 3 cases of myocardial infarction mentioned above. Cardiotoxicity was not reported in phase III and IV studies of erlotinib for NSCLC.2,3) however, coronary artery events, including myocardial infarction, were reported in 2.3% of patients receiving erlotinib combined with gemcitabine compared to 1.2% in patients receiving gemcitabine alone for pancreatic cancer.7) Thus, oncologists and cardiologists should be vigilant about the potential for erlotinib-induced adverse cardiovascular events.

In the present case, it was expected that continued administration of erlotinib would exacerbate heart failure, but close monitoring and treatment of heart failure by a cardiologist allowed the administration of erlotinib to be continued. There is controversy as to whether anticancer drugs should be continued when cardiovascular complications appear. Leong, et al.8) reported that in women with breast cancer in whom trastuzumab caused mild cardiotoxicity, a strategy of continuing trastuzumab in combination with heart failure therapy permitted the uninterrupted use of trastuzumab in 90% of patients, and all patients had improved LV EFs. Thus, treatment of heart failure with intensive monitoring may allow patients with mild cardiotoxicity to continue anticancer treatment. When cardiovascular complications appear, it is important to provide the best treatment for patients by close collaboration between oncologists and cardiologists.

The underlying mechanism of erlotinib-induced cardiotoxicity remains unclear. EGFR signaling itself is protective in the setting of catecholamine excess in a mouse model.9) Pharmacological inhibition of EGFR with erlotinib causes dilated cardiomyopathy following chronic catecholamine infusion in mice.9) In heart failure, enhanced levels of norepinephrine resulting from activation of the sympathetic nervous system lead to chronic stimulation of cardiac β1-adrenergic receptors.10) Stimulation of β1-adrenergic receptors induces EGFR transactivation to activate pro-survival signaling pathways in cardiomyocytes.9) Therefore, erlotinib may block the cardioprotective signals through EGFR inhibition in situations of excessive catecholamine secretion, leading to the development of heart failure. Our patient had stage IV lung cancer, and her general condition was poor as a result of persistent poor eating due to prolonged stomatitis caused by gefitinib administered prior to erlotinib. Therefore, her sympathetic nerve activity may have been high, and the signals mediated by EGFR could have played an important role in cardioprotection. Thus, it is necessary to consider the possibility of development of heart failure when using EGFR inhibitors in patients who are likely to have high sympathetic nerve activity. Conversely, β-blockers could be effective in patients with EGFR inhibitor-induced heart failure because sympathetic nerve activity may be enhanced in patients with cardiac dysfunction. Our patient was administered a β-blocker, and erlotinib could be continued for a long period without exacerbation of heart failure (Figure 4).

In summary, this rare case of erlotinib-induced cardiomyopathy highlights the possible cardiotoxic effects of
erlotinib and suggests the need for close clinical and echocardiographic follow-up of these patients.

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**Disclosure**

**Conflicts of interest:** The authors declare no conflicts of interest.

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