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CASE REPORT

INTERMEDIATE

CLINICAL CASE SERIES

Osimertinib-Induced Cardiomyopathy

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ABSTRACT

Osimertinib is the preferred treatment in patients with metastatic non-small cell lung cancer with epidermal growth factor receptor mutations. We report a case series of acute cardiomyopathy with heart failure exacerbation during osimertinib treatment. We suggest that cardiotoxicity from osimertinib is reversible and occurs at a dose of 80 mg/day. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:641-5) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cancer treatment has evolved considerably in the past 30 years with the advent of targeted therapies. A recent study reported osimertinib as the superior agent for the treatment of non-small cell lung cancer (NSCLC) compared with first- and second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) (1). Data from osimertinib clinical trials showed that 2.6% of 1,142 patients on osimertinib developed cardiomyopathies, 0.1% of which were fatal, with 3.9% of 908 osimertinib-treated patients developing a >10% decrease in ejection fraction (EF) or EF <50% (2-5). A recent analysis of U.S. Food and Drug Administration Adverse Events Reporting System demonstrated that osimertinib had higher rates of QT prolongation, cardiac failure, and atrial fibrillation in comparison with other EGFR-TKIs (6). Since 2017, there have been several cases reports of osimertinib-induced cardiomyopathy. Some of these patients presented with symptomatic heart failure, while others were found to have depressed EFs on surveillance echocardiography.

As osimertinib is being used as a first-line agent, and increased survival is associated with targeted therapy in the treatment of NSCLC, further characterization of adverse effects is needed. For this purpose, we present 3 cases of osimertinib-induced cardiomyopathy and a review of the existing research.

LEARNING OBJECTIVES

- To broaden the differential diagnosis of patients presenting with heart failure after the initiation of osimertinib.
- To understand the role of routine echocardiographic surveillance in patients initiated on osimertinib for NSCLC.
- To characterize the dosage at which osimertinib-induced cardiomyopathy occurs, along with the natural history of this cardiomyopathy.

CASES

CASE 1. An 84-year-old woman with coronary artery disease status post coronary artery bypass graft and prior ischemic stroke was diagnosed in 2018 with stage IVa adenocarcinoma of the lung with an EGFR

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ABBREVIATIONS AND ACRONYMS

CHF = congestive heart failure

EF = ejection fraction

EGFR = epidermal growth factor receptor

NSCLC = non-small cell lung cancer

TKI = tyrosine kinase inhibitor

mutation (L858R mutation on exon 21). She was placed on osimertinib 40 mg/day for 7 months. Subsequent staging chest computed tomography showed disease progression, and osimertinib dosing was increased to 80 mg/day. Four weeks after dose escalation, she presented with acute hypotension, hyponatremia, and blood pressure of 147/86 mm Hg. Repeat chest computed tomography showed moderate to large bilateral pleural effusions and associated septal thickening, suggestive of pulmonary edema (**Figure 1**). N-terminal pro-brain natriuretic peptide was significantly elevated at 22,579 pg/ml. Acute coronary syndrome was ruled out with no change in troponin T (from 29 to 31 ng/l), and no ischemic ECG changes. Echocardiography showed a left ventricular EF of 20%, with severe global left ventricular hypokinesis (previous echocardiography showed an EF of 63%). Osimertinib treatment was stopped, and she was started on furosemide, losartan, and bisoprolol for cardioprotection and symptomatic treatment. Four weeks later, she was clinically euvolemic, and furosemide was discontinued. Echocardiography was repeated shortly after this visit and showed improvement of EF to 41%. She was subsequently initiated on erlotinib 100 mg/day, with no recurrence of congestive heart failure (CHF) symptoms.

CASE 2. A 71-year-old man with atrial fibrillation, hypertension, hyperlipidemia, and recurrent adenocarcinoma of the lung with EGFR mutations (G719C and S768I) was initiated on osimertinib 80 mg/day. Twelve days later, he presented to the emergency department with acute-onset dyspnea and lower extremity edema. He was hypoxic to 86% on 6 l supplemental oxygen, with blood pressure of 108/73 mm Hg. Chest computed tomography showed findings suggestive of pulmonary edema. N-terminal pro-brain natriuretic peptide was elevated at 2,138 pg/ml. Electrocardiography showed atrial fibrillation with a rapid ventricular rate at 140 beats/min. Troponins were found to be rising from 329 to 843 ng/l. Echocardiography performed on admission showed an EF of 39%, global hypokinesis, and moderate left ventricular enlargement (Videos 1 and 2). Echocardiography 2 months previously demonstrated an EF of 52% (Videos 3 and 4). Pleural studies indicated a transudative effusion. A diagnosis of acute heart failure was made. The patient was subsequently diuresed, and osimertinib treatment was stopped. He was initiated on treatment with lisinopril and metoprolol daily. As the association between the initiation of osimertinib and the patient's CHF exacerbation was not completely clear given the confounding factors of his tachycardia, he was rechallenged with osimertinib daily once his clinical status improved back to baseline. Since reinitiating osimertinib, he has not had further exacerbation of his cardiac symptoms.

CASE 3. A 72-year-old woman with no known modifiable cardiac risk factors was found to have recurrent adenocarcinoma of the lung. She carried an EGFR mutation at exon 19 and was started on osimertinib 80 mg/day. One month later, she presented to the emergency department with progressive dyspnea. En route to the emergency department, she was hypoxic to 75% on room air and was started on bilevel positive airway pressure. Blood pressure was 157/80 mm Hg and chest x-ray demonstrated moderate right pleural effusion and pulmonary edema. Echocardiogram revealed an EF of 38% (prior EF: 67%). N-terminal pro-brain natriuretic peptide was elevated at 7,306 pg/ml. The patient was diagnosed with acute heart failure and initiated on treatment with an angiotensin-converting enzyme inhibitor and a beta-blocker. Osimertinib was discontinued, and the patient was diuresed. Follow-up echocardiography 2 months later demonstrated normalization of EF to 57%. She was ultimately switched to erlotinib for further management of her lung cancer, with no recurrence of CHF symptoms.

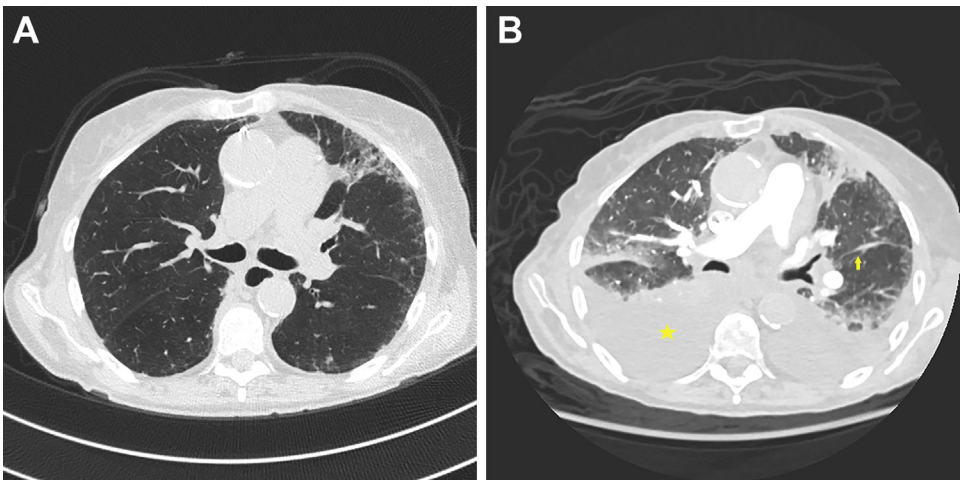
DISCUSSION

Osimertinib is a third-generation EGFR TKI approved for locally advanced or metastatic NSCLC if a T790M mutation is present in the EGFR gene (7). As therapies are evolving and survivorship is increasing in patients with cancer, it is vital to recognize and characterize the short-and long-term cardiac toxicities seen in these patients.

Our case series and review of the published research demonstrate the dosage at which the cardiomyopathy manifests and the benefits of cardioprotective medications on improving EF and suggests that replacement with erlotinib does not exacerbate cardiomyopathy. Additionally, these cases illustrate how patients present with osimertinib-induced cardiomyopathy.

Eleven cases of osimertinib-induced cardiomyopathy have been described (**Table 1**). A review of the 7 patients who underwent follow-up echocardiography after drug cessation showed improvement of EF after cessation of osimertinib in 6 patients. This indicates that cardiotoxicity from osimertinib is likely reversible, albeit with cardioprotective therapy. In our case series, cardioprotective therapy was defined as beta-blocker and angiotensin-converting enzyme inhibitor therapy up-titrated as tolerated, with adjunct

FIGURE 1 Computed Tomography of the Chest Demonstrating Pulmonary Sequela of Heart Failure



(A) Prior to dose escalation from 40 to 80 mg osimertinib. **(B)** Pulmonary edema **(arrow)** and bilateral effusions **(star)** 4 weeks after osimertinib dose escalation.

medications for CHF (diuretic agents, aldosterone inhibitors) as indicated.

Although the mechanism of myocyte injury is well characterized with anthracyclines (8), the underlying pathophysiology of cardiotoxicity in human epidermal growth factor receptor 2 (HER2)/EGFR-targeted therapies is not entirely understood. HER2-knockout mice studies have demonstrated 50% reduction in heart contractility with severe dilated cardiomyopathy, which illustrates the importance of HER2 in normal cardiac physiology (8,9). It is important to note that EGFR/ErbB1 and HER2/ErbB2 are in the same family of tyrosine kinase receptors that are crucial in cell signaling for cell differentiation, proliferation, motility, and apoptosis (10). Although there is limited evidence describing the effects of the EGFR/ErbB1 signaling path on myocyte injury, some theorize that "the cardiotoxic effects observed in ErbB1-targeted interventions may be an indirect manifestation of impaired ErbB2 signaling," as ErbB2 and ErbB1 often dimerize (11).

Additionally, all reported cases with known dosing levels indicated the development of cardiac dysfunction at a dose of 80 mg of osimertinib (12–15). In one of our cases presented here, the patient was initially started on 40 mg of osimertinib for 7 months, with no evidence of cardiac dysfunction on the basis of symptoms. Four weeks after her dose was escalated to 80 mg/day, she presented in acute heart failure. Although dose reduction can potentially be considered to prevent initial or recurrent cardiotoxicity, the FLAURA clinical trial results, which guide the clinical use of osimertinib, were based on therapy at 80 mg/day (1).

A review of the published research demonstrates a possible benefit of routine echocardiographic surveillance and the creation of a registry to document these adverse events. Of the 3 asymptomatic patients with reduced EFs detected on routine echocardiography, the reduction in EF was lower, and all returned to baseline EF. At this time, there are no standardized recommendations for surveillance echocardiography unless patients are symptomatic, despite recommendations included in the investigator brochure and U.S. Food and Drug Administration drug label for osimertinib (5). We hope that our case series and review will bring awareness of this complication and demonstrate the importance of routine surveillance echocardiography in patients on osimertinib. Consideration of global longitudinal strain screening may arise in the future as studies emerge providing data on strain imaging in these patients, similar to those with anthracyclines or trastuzumab.

The benefits of frontline osimertinib include improvement of progression-free survival and overall survival, greater intracranial efficacy, and better tolerability (1). In our patients, osimertinib was discontinued and treatment was switched to a first-generation EGFR TKI. As we learn more about the cardiac adverse events of these new agents, we recommend developing multidisciplinary teams that would guide the heart failure treatment of these patients, and after their cardiac complications are optimally treated, cancer care teams could consider

TABLE 1 Clinical Features of Patients With Osimertinib-Induced Cardiomyopathy

First Author (Year)	Age (yrs)/Sex	Primary Tumor	Osimertinib Dose	Time From Initiation of Osimertinib to Symptoms of HF	Echocardiography	NYHA Functional Class	History of CAD	Pre-Osimertinib EF (%)	Post-Osimertinib EF (%)	Improvement in EF After Cessation of Drug?	Reinitiation of Osimertinib?
Watanabe et al. (2017)	78/F	NSCLC	Unknown	3 weeks	LA dilatation without any wall motion asynergy	—	No	Unknown	Unknown	Unknown	Unknown
Oyakawa et al. (2017)	84/F	NSCLC	80 mg	34 weeks	Dilated and diffusely hypocontractile left ventricle	II	No	Unknown	33	No	No
Okutucu et al. (2018)	64/F	NSCLC	Unknown	8 weeks	Depressed LV systolic function	—	No	Unknown	24	Unknown	No
Reale et al. (2018)	70/M	NSCLC	80 mg	8 weeks	Moderate increase in LA volume without LV dilatation	II–III	No	60	45	No	NA (deceased)
Reale et al. (2018)	73/F	NSCLC	80 mg	60 weeks*	Global LV dysfunction	I	No	62	50	Yes	Yes
Reale et al. (2018)	47/F	NSCLC	80 mg	72 weeks*	No change in left chamber volume or diastolic function	I	No	64	51	Yes	Yes
Reale et al. (2018)	71/F	NSCLC	80 mg	48 weeks	LA and LV dilation	II–III	No	58	45	Yes	Yes
Reale et al. (2018)	80/F	NSCLC	80 mg	44 weeks*	LA and LV dilation	I	No	62	43	Yes	Yes
Present case 1	85/F	NSCLC	80 mg	32 weeks	Severe generalized LV hypokinesis with akinesis of the mid anterolateral and mid inferolateral segments	II–III	Yes	63	28	Yes	No
Present case 2	71/M	NSCLC	80 mg	12 days	Moderate LV enlargement and global hypokinesis	II–III	Yes	52	39	Unknown	Yes
Present case 3	72/F	NSCLC	80 mg	4 weeks	Basal and mid regional wall motion abnormalities, with preserved apex	II–III	No	67	38	Yes	No

*Asymptomatic patient (reduced EF on routine echocardiography).

EF = ejection fraction; HF = heart failure; LA = left atrial; LV = left ventricular; NA = not available; NSCLC = non-small cell lung cancer; NYHA = New York Heart Association.

reinitiation of osimertinib or rechallenging patients with osimertinib after progression on the first- or second-generation EGFR TKI or patients with T790M mutations, understanding the risk for cardiac decompensation.

Studying osimertinib-induced cardiomyopathy in our patients has several limitations. The retrospective nature of case series, as well as selection bias, is important to note. Additionally, 2 of our patients' multiple comorbidities could have worsened their EFs and served as confounding factors. Nevertheless, the timing between the initiation of chemotherapy and manifestation of symptoms points toward osimertinib-induced cardiomyopathy as the cause of presentation in all 3 patients in our case series.

TAKE-HOME MESSAGE

These cases highlight a rare but important cause of chemotherapy-induced cardiomyopathy that needs to be considered in patients who have started treatment with osimertinib. Our case series suggests that the cardiomyopathy occurs at daily dose of 80 mg of osimertinib. Additionally, our cases illustrate the benefits of cardioprotective medications such as beta-blockers and angiotensin-converting enzyme inhibitors on improving EF. The cases also suggest that replacing osimertinib with erlotinib does not exacerbate cardiomyopathy.

Osimertinib is recommended as a first-line therapy for patients with NSCLC who have targetable EGFR mutations. It is imperative that we closely monitor these patients for cardiotoxicity, given the high rate of morbidity and mortality with these complications. This study demonstrates the importance of collaboration in cardio-oncology as an emerging multidisciplinary subspecialty to improve the care of patients with cancer as new cardiotoxic therapies arrive on the market.

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KEY WORDS cardiotoxicity, cardio-oncology, heart failure, osimertinib, reduced ejection fraction

APPENDIX For supplemental videos, please see the online version of this article.