VOL. 5, NO. 6, 2023
ISSN 2666-0873

# Letters

RESEARCH LETTER

## Osimertinib-Associated Cardiomyopathy In Patients With Non-Small Cell Lung Cancer

### A Case Series

Non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations can be effectively treated with EGFR tyrosine kinase inhibitors (TKIs). Clinical trials have demonstrated improved survival with the EGFR-TKI osimertinib, as well as an increased incidence of heart failure with reduced ejection fraction during treatment.[1] The objective of this study was to characterize the patient phenotype of those who develop cardiomyopathy after initiating osimertinib.

This was a single-center retrospective case series approved by the institutional review board at Stanford University utilizing the Stanford Medicine Research Data Repository (STARR) for cohort screening, followed by manual chart review and abstraction of study variables from the electronic health record. Patients analyzed were: 1) prescribed osimertinib for EGFR-mutant NSCLC of any stage in the STARR database from January 1, 2016 to June 1, 2022 (N = 862); 2) had an ICD-10 code for acute systolic heart failure and developed a new reduction in the left ventricular ejection fraction (LVEF) of at least 10% to an absolute value of ≤50% (with or without symptoms) while taking osimertinib; and 3) were determined by treating clinicians to have osimertinib as the suspected cause of new cardiomyopathy. The records of all patients meeting these criteria (N = 23) were manually reviewed, and 6 patients were excluded due to alternative etiologies of heart failure (arrhythmia [n = 2], acute coronary syndrome [n = 3], and cardiac tamponade [n = 1]). In the remaining 17 patients, osimertinib was determined to be the possible or probable cause of heart failure.

The median age of the patients was 72 years (Q1-Q3: 65-79 years), 12 of 17 patients (70.6%) were female, 11 of 17 patients were Asian (64.7%), and the median of the body mass index was 20.7 kg/m$^2$ (Q1-Q3: 18.7-23.9 kg/m$^2$). Ten (58.8%) had at least 3 cardiac risk factors including: 15 of 17 (88.2%) with hypertension, 10 of 17 (58.8%) with hyperlipidemia, 8 of 17 (47.1%) with atrial fibrillation, 5 of 17 (29.4%) with coronary artery disease, 3 of 17 (17.6%) with pre-existing cardiomyopathy, 3 of 17 (17.6%) with diabetes, 2 of 17 (11.8%) with history of smoking, 1 of 17 (5.9%) with chronic kidney disease, and 1 of 17 (5.9%) with stroke. Sixteen (94.1%) had Stage IV NSCLC at the time of osimertinib initiation; 7 of 17 (41.2%) were previously treated with cytotoxic chemotherapy, predominantly platinum agents and antimetabolites. Three patients (17.6%) had previous bevacizumab treatment. None were treated with anthracyclines or anti-human epidermal growth factor receptor (HER2) agents. All patients had diagnostic testing for alternative causes of cardiomyopathy that did not suggest another etiology. Fourteen (82.4%) were evaluated by cardiologists, with osimertinib attributed as the etiology of LVEF reduction in all. Three patients (17.6%) were managed by other subspecialists (pulmonology, oncology), with osimertinib attributed as the cause in all. Using the Naranjo Adverse Drug Reaction assessment tool, we determined osimertinib as the "possible" cause of cardiomyopathy in 13 of 17 patients (76.5%), and "probable" in 4 of 17 patients (23.5%).[2]

In 9 of 17 patients (52.9%), an echocardiogram was obtained for workup of new or worsening symptoms; in the remaining 8 of 17 patients (47.1%), an echocardiogram was obtained as a screening measure after starting osimertinib. The median magnitude of LVEF reduction was −22.0 (Q1-Q3: −14.0 to −32.0), occurring at a median of 4.2 months (Q1-Q3: 3.3-9.4 months) after starting osimertinib. Two had Takotsubo syndrome, which has been associated with malignancy and osimertinib.[3] Nine (52.9%) had NYHA functional class III symptoms at diagnosis; all 9 required hospitalization. Fourteen patients (82.4%) were referred to a cardiologist because of the reduction in LVEF. Cardiac interventions in the 6 months following LVEF reduction included 23 heart failure medication changes (**Table 1**) in 14 of 17 (82.4%) patients, and device implantations in 2 of 17 (11.8%) patients. Osimertinib was discontinued in 13 of 17 patients (76.5%), and 7 of 13 patients (53.8%)

JACC: CARDIOONCOLOGY, VOL. 5, NO. 6, 2023
DECEMBER 2023:839–841

**TABLE 1 Cardiovascular Outcomes**

| | |
|---|---|
| Reason for obtaining TTE | |
| Symptoms | 9/17 (52.9) |
| Screening measure | 8/17 (47.1) |
| Time between osimertinib initiation and LVEF decrease, mo | 4.2 (3.3-9.4) |
| Magnitude, LVEF decrease, % points | −22.0 (−14.0 to −32.0) |
| Osimertinib discontinued for LVEF decrease | 13/17 (76.5) |
| NYHA functional class during LVEF decrease | |
| I | 4/17 (23.5) |
| II | 4/17 (23.5) |
| III | 9/17 (52.9) |
| IV | 0/17 (0) |
| Heart failure prescription after LVEF decrease | 14/17 (82.4) |
| Diuretic | 5/17 (29.4) |
| Beta-blocker | 7/17 (41.2) |
| RAAS inhibitor | 8/17 (47.1) |
| SGLT2 inhibitor | 0/0 (0) |
| Mineralocorticoid antagonist | 1/17 (5.9) |
| Digoxin | 2/17 (11.8) |
| Device implantation after LVEF decrease | 2/17 (11.8) |
| Cardiology referral after LVEF decrease | 14/17 (82.4) |
| Hospitalization after LVEF decrease | 9/17 (52.9) |
| LVEF recovery after osimertinib discontinuation | 7/13 (53.8) |
| Death | 12/17 (70.6) |
| Time after LVEF decrease to death, mo | 3.2 (1.7 to 18.4) |
| Death within 90 days of LVEF decrease | 5/12 (41.7) |
| Suspected cardiac death | 3/12 (25.0) |
| Naranjo scale | |
| Unlikely, 0 | 0/17 (0) |
| Possible, 0-4 | 13/17 (76.5) |
| Probable, 4-8 | 4/17 (23.5) |
| Certain, 9+ | 0/17 (0) |

Values are n/N (%) or median (Q1-Q3).

LVEF = left ventricular ejection fraction; RAAS = renin angiotensin aldosterone system; SGLT2 = sodium-glucose cotransporter 2; TTE = transthoracic echocardiography.

experienced LVEF recovery of at least 10% within 12 months of discontinuation. Mortality occurred in 12 of 17 patients (70.6%) at the time of data analysis, 10 of whom died a median of 3.2 months (Q1-Q3: 1.7-18.4 months) after discontinuation of osimertinib. Five deaths occurred within 90 days of LVEF reduction and prompt discontinuation of osimertinib. One died during her index heart failure hospitalization secondary to respiratory failure from pulmonary edema and advanced lung malignancy. Among 13 who discontinued osimertinib, 9 patients died in the setting of cancer progression or being transitioned to hospice. In the 4 patients who continued osimertinib after their LVEF declined, 2 died of progression and 2 remain alive. This calculated raw proportion of patients who died was higher than the patients who did not meet case criteria (337 of 845 patients, 39.8%).

We identified 17 cases of cardiomyopathy suspected to be related to osimertinib. Cardiac risk factors were common, which limits the generalizability of data. However, the data do provide a "real world" survey of osimertinib-associated cardiomyopathy, providing more information about this relevant cardiotoxicity. In contrast to most existing studies on osimertinib cardiotoxicity,[4,5] we provide detailed clinical and longitudinal outcome data. We were not able to establish with certainty that osimertinib was the etiology of reduced LVEF in all cases; however, we utilized a validated adverse drug assessment tool, and all cases were felt to be at least attributable to the drug.

Although no guideline recommendations exist currently, periodic monitoring of the LVEF is suggested in the osimertinib package labeling. In this study, 8 of 17 patients received surveillance echocardiograms, whereas 9 of 17 had echocardiograms in response to symptoms. The identification of cardiomyopathy resulted in significant changes to management with heart failure medication changes in 14 of 17 patients in the 6 months after diagnosis. In 2 patients, ICD implantation or CRT therapy was implemented. Nine patients required hospitalization at the time of LVEF reduction, suggesting a more severe clinical phenotype than previously recognized. These findings suggest potential future utility of routine surveillance echocardiography; however, which patients would benefit from routine surveillance remains to be determined and should be defined by prospective studies.

Our patient demographics were relatively homogenous, and larger populations should be studied in the future. Mortality was high in this cohort; however, these data must be interpreted with caution given advanced NSCLC in the cases identified. Qualitatively, patients who discontinued osimertinib experienced cancer progression, and we recognize the large volume of randomized data demonstrating improved lung cancer outcomes with osimertinib as a key consideration when encountering osimertinib cardiotoxicity.

**Miguel J. Franquiz, PharmD, MD**
**Sarah Waliany, MD, MS**
**Audrey Yingwei Xu**
**Anna Hnatiuk, MD, PhD**
**Sean M. Wu, MD, PhD**
**Paul Cheng, MD, PhD**
**Heather A. Wakelee, MD**
**Joel Neal, MD, PhD**
**Ronald Witteles, MD**
***Han Zhu, MD**

*Stanford Medicine
240 Pasteur Drive

Room 3500
Biomedical Innovations Building
Stanford, California 94304, USA
E-mail: hanzhu@stanford.edu
@HanZhuMD

https://doi.org/10.1016/j.jaccao.2023.07.006



Dr Wu is supported by the Joan and Sanford I Weill Scholar Award. Dr Cheng is supported by American Heart Association grant 20CDA35310303 and National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute grant K08-HL153798. Dr Zhu is supported by NIH grant 1K08HL16140501. Dr Wu receives consulting fees from AstraZeneca. Dr Neal serves as an advisory board participant for AstraZeneca. Dr Wakelee receives support from AstraZeneca. Dr Witteles serves as an advisory board participant for Pfizer, Alnylam, Ionis, AstraZeneca, Janssen, Intellia, Novo Nordisk, and Alexion. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors thank the entire Stanford Cardio-Oncology team (cardiology and oncology) for their dedicated clinical care of osimertinib-treated patients and for providing access to the data for analysis.

Joshua D. Mitchell, MD, MSCI, served as Guest Associate Editor and Paaladinesh Thavendiranathan, MD, MSc, served as Guest Editor-in-Chief of this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

## REFERENCES

**1.** Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum–pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376(7):629–640.

**2.** Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.

**3.** Fukuda Y, Kawa Y, Nonaka A, et al. Reoccurrence of takotsubo cardiomyopathy induced by osimertinib: a case report. *Clin Case Rep*. 2022;10(9):e6279.

**4.** Anand K, Ensor J, Trachtenberg B, et al. Osimertinib-induced cardiotoxicity. *J Am Coll Cardiol CardioOnc*. 2019;1(2):172–178.

**5.** Ewer M, Tekumalla S, Walkding A, et al. Cardiac safety of osimertinib: a review of data. *J Clin Oncol*. 2021;39(4):328–337.