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CLINICAL CASE CHALLENGES

Heart Failure Associated With the Epidermal Growth Factor Receptor Inhibitor Osimertinib

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Incorporation of molecular targeted therapies into the care of patients with sensitizing mutations has driven significant improvements in outcomes in non-small cell lung cancer (NSCLC). Epidermal growth factor receptor (*EGFR*)-mutant lung cancer includes the greatest percentage of these cases, and accounts for approximately 15% of lung adenocarcinoma cases in the United States (1). Following the FLAURA (AZD9291 Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer) trial, osimertinib, a third-generation oral irreversible EGFR tyrosine kinase inhibitor (TKI), became part of first-line therapy for *EGFR*-mutant lung cancer. Although generally well-tolerated, emerging evidence suggests that treatment with osimertinib can result in significant cardiac toxicity (2–4). We present here a case of heart failure in a patient treated with osimertinib who improved following cessation of therapy (**Figure 1**).

CASE DESCRIPTION

A 67-year-old woman with history of hypertension, hypothyroidism, pulmonary embolism treated with enoxaparin, and metastatic EGFR-mutant lung adenocarcinoma was treated with 4 cycles of platinum-based chemoradiation for stage III disease in 2010. In 2012, the cancer recurred, and she was started on the first-generation EGFR TKI erlotinib, which she tolerated well with disease control from May 2012 until September 2018, when her disease progressed in the form of a painful new vertebral lesion. Although circulating tumor DNA did not show evidence of a resistant clone (i.e., T790M mutation), she was transitioned to osimertinib in September 2018 because of the likelihood that disease progression was due to this common mechanism of resistance. An electrocardiogram (ECG) obtained shortly before osimertinib initiation revealed normal sinus rhythm with a normal QRS duration and normal corrected QT interval. There was no evidence of baseline conduction disease. A transthoracic echocardiogram (TTE) previously obtained in March 2016 demonstrated a left ventricular ejection fraction (LVEF) of 70% with left ventricular end-diastolic dimension normal at 35 mm. Global longitudinal strain was not measured on this previous study. Following initiation of osimertinib, the patient improved clinically and radiographically, with her first monitoring imaging studies revealing stable to improved burden of metastatic disease. ECGs obtained in October and November 2018 demonstrated no significant changes attributable to osimertinib.

In April 2019, 7 months after osimertinib initiation, she presented with shortness of breath and was diagnosed with heart failure. Her ECG demonstrated sinus rhythm and a left bundle branch block that was new

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

EGFR = epidermal growth factor receptor

LVEF = left ventricular ejection fraction

NRG = neuregulin

NSCLC = non-small cell lung cancer

TKI = tyrosine kinase inhibitor

TTE = transthoracic echocardiography

compared with a previous tracing obtained in November 2018. There was no significant prolongation of the corrected QT interval. Troponin was repeatedly negative, although brain natriuretic peptide was elevated at 1,104 pg/ml (normal: 0 to 353 pg/ml). A TTE demonstrated decreased LVEF (42% by quantitative biplane measurement) with global hypokinesis, abnormal global longitudinal strain (−12%), septal dyssynchrony, and mild biventricular dilation, findings that were all new compared with the previous TTE obtained in March 2016. A pharmacological nuclear stress test at that time demonstrated a LVEF of 35% with normal perfusion. Lisinopril and metoprolol succinate were initiated, although metoprolol was subsequently discontinued due to fatigue, and lisinopril was replaced by valsartan/sacubitril.

A follow-up TTE in June 2019, while still on osimertinib, demonstrated that her LVEF had decreased to 24%. Cardiac magnetic resonance imaging subsequently confirmed severe left ventricular systolic dysfunction with no late gadolinium enhancement to suggest focal fibrosis or scar and no evidence of myocarditis. In the absence of alternative explanations, osimertinib-associated cardiotoxicity was considered to be the most likely etiology. Osimertinib was discontinued, with subsequent positron emission tomography–computed tomography demonstrating several new and worsening sites of osseous progression without evidence of visceral progression. A repeat TTE performed 12 weeks after osimertinib cessation showed some improvement in LVEF to 34%, at which time erlotinib was restarted.

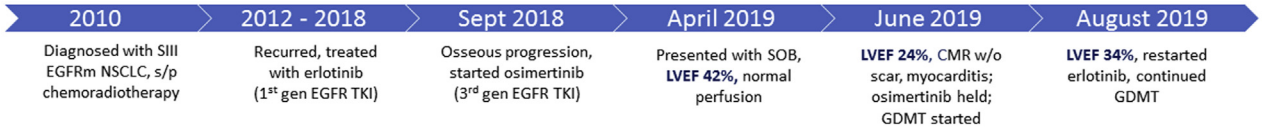
Her LVEF was stable 4 weeks after resuming erlotinib, and since then, she has been asymptomatic from a heart failure perspective. Further optimization of guideline-directed medical therapy has been limited by hypotension. A post-progression iliac biopsy did not reveal evidence of either erlotinib resistance (e.g., a T790M mutation) or a targetable mechanism of resistance. She currently remains clinically stable on erlotinib, having also undergone palliative radiation to sites of painful osseous progression. If further symptomatic progression occurs, the plan is to recommend a transition to cytotoxic chemotherapy.

DISCUSSION

The first reported case of heart failure with reduced LVEF with osimertinib developed within 3 weeks of starting therapy (5), whereas our patient presented with symptoms of heart failure 7 months after initiation. ECGs and TTE obtained before osimertinib initiation were not suggestive of baseline conduction disease or subclinical cardiomyopathy. At the time of her diagnosis of heart failure, a comprehensive evaluation consisting of ECG, TTE, pharmacological nuclear stress testing, and cardiac magnetic resonance imaging confirmed that there was no evidence of ischemic or inflammatory injury to the myocardium, which suggested osimertinib as the only identifiable offending agent. Some recovery in LVEF was observed following osimertinib cessation, albeit while simultaneously initiating guideline-directed therapy for nonischemic cardiomyopathy. Her LVEF has subsequently remained stable following resumption of erlotinib as post-progression therapy.

Although generally well-tolerated, there is increasing evidence that osimertinib may be uniquely cardiotoxic compared with earlier generation EGFR TKIs. Osimertinib gained approval by the Food and Drug Administration for use in the first-line setting for EGFR-mutant NSCLC following the phase III FLAURA study, which demonstrated superior progression-free survival and improved tolerability versus first-generation EGFR TKIs (erlotinib and gefitinib). In this study, 10% of patients developed QTc prolongation on osimertinib compared with 5% as previously reported with first-generation TKIs (2). The FLAURA study reported a single case of cardiac failure as a serious adverse effect of osimertinib (<1% of 279 patients). In contrast, 5% of patients in the osimertinib arm of the AURA3 (AZD9291 [Osimertinib] Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer) trial experienced an LVEF decline of >10% and a decline to <50% (14 of 258 patients) (3). Of these, 3% (6 of 258 patients) developed clinically significant heart failure. More recently, a retrospective review of data from the Food and Drug Administration Adverse Event Reporting System database described a number of cardiovascular events associated with osimertinib use, including heart failure, atrial fibrillation, and QT prolongation (4). In this review, heart failure was twice as likely to develop in patients treated with osimertinib versus other EGFR TKIs (reporting odds ratio: 2.2; 95% confidence interval: 1.5 to 3.2). Because of increasing evidence that osimertinib affects the conduction system, it remains unclear in our case whether osimertinib treatment could have caused heart failure indirectly through the development of left bundle branch block and mechanical dyssynchrony or through direct effects on the myocardium. Although left bundle branch block has not been reported in published studies of

FIGURE 1 Case Timeline

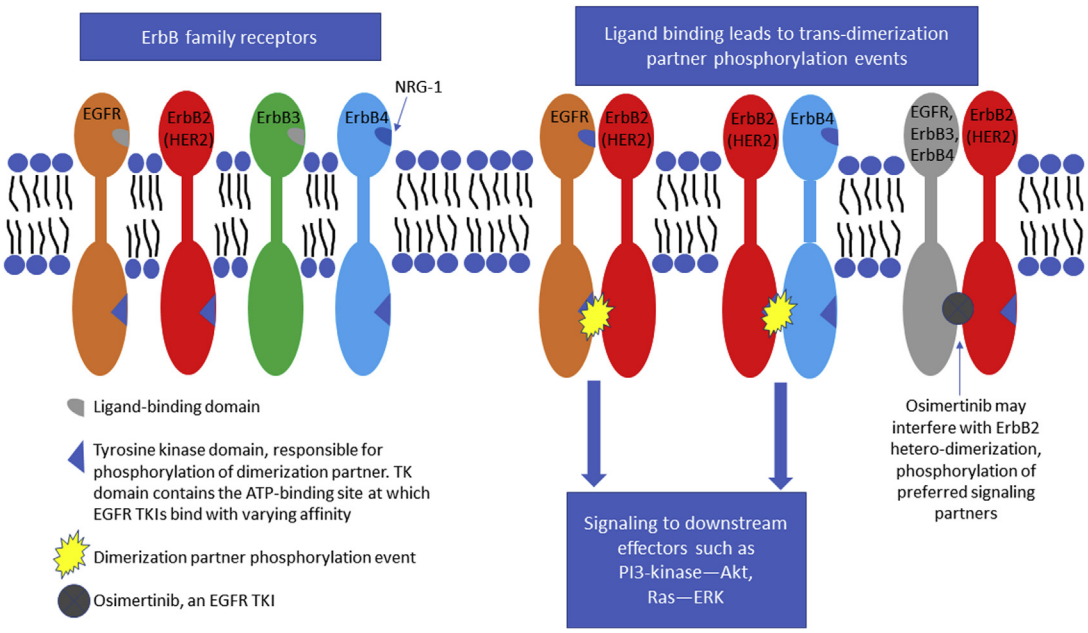


Key clinical events are presented in chronological order outlining oncological diagnosis, timing of therapy, and development of cardiac toxicity. CMR = cardiac magnetic resonance imaging; EGFR = epidermal growth factor receptor; GDMT = guideline directed medical therapy; gen = generation; LVEF = left ventricular ejection fraction; NSCLC = non-small cell lung cancer; SOB = shortness of breath; TKI = tyrosine kinase inhibitors.

osimertinib, it is possible that QT prolongation in some patients occurred in the setting of QRS prolongation, an area worthy of further investigation.

Although a mechanistic explanation for the cardiotoxicity of osimertinib is currently lacking, perturbation of neuregulin (NRG)-1/ErbB signaling with agents such as trastuzumab is well-associated with cardiomyopathy. The NRG-1/ErbB axis mediates the cardiac myocyte response to stress via Akt-dependent anti-apoptotic effects and other mechanisms (6). ErbB family receptors are activated by ligands such as NRG-1, leading to phosphorylation of homo- and/or heterodimerization partners and ultimately downstream signaling to Ras–ERK and PI3-kinase–Akt pathways (**Figure 2**). Trastuzumab disrupts this axis by preventing ErbB4 (activated by NRG-1) from heterodimerizing with ErbB2 (HER2), a preferred signaling partner (7). Although osimertinib is highly specific for ErbB1 (EGFR), mouse models have demonstrated greater inhibition of wild-type ErbB2 (HER2) than that observed with erlotinib or afatinib (8). Whether this effect is responsible for increased cardiotoxicity requires further exploration. If the mechanism of myocardial injury is similar to that observed with

FIGURE 2 ErbB Family Receptor Signaling



ErbB family receptors are stimulated by several ligands including neuregulin (NRG)-1, which leads to homo- and/or hetero-dimerization of ErbB receptors and downstream signaling to PI3-kinase–Akt and Ras–ERK. Disruption of ErbB4 heterodimerization with ErbB2 by trastuzumab impairs downstream signaling and normal cardiac myocyte stress response. Osimertinib may interfere with cardiovascular function through its affinity for the wild-type ErbB2 receptor. ATP = adenosine triphosphate.

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other HER2-directed therapies, cessation of therapy alone or initiation of neurohormonal therapy may result in recovery of systolic function (9).

CONCLUSIONS

As demonstrated by this case, we currently lack diagnostic findings specific for osimertinib-associated cardiotoxicity, which remains a diagnosis of exclusion. The Food and Drug Administration label for osimertinib suggests obtaining baseline and on-treatment LVEF assessment only in patients with known cardiac risk factors. The label also recommends initiating a cardiac evaluation in patients on osimertinib who present with new symptoms potentially attributable to heart failure. Further investigation is needed to understand the risk factors for and mechanism by which osimertinib induces cardiomyopathy in a small number of patients. Until then, clinicians must be aware of the potentially serious but uncommon risk of cardiotoxicity from an otherwise well-tolerated and highly effective therapy.

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