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EDITORIAL COMMENT

Targeting the Cardiotoxicity of Epidermal Growth Factor Receptor Inhibitors*

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Targeted therapies have revolutionized the treatment of non-small-cell lung cancer (NSCLC). Despite a common histology, adenocarcinomas of the lung result from a broad spectrum of oncogenic drives including: *KRAS*, *EGFR*, *ALK*, *ROS1*, *BRAF*, and *NTRK1* (1). Small molecule inhibitors have been developed to target many of these drivers, and many have received Food and Drug Administration approval. Epidermal growth factor receptor (EGFR) inhibitors have been available the longest and at the vanguard of the targeted therapy approach to lung cancer. The first generation of EGFR inhibitors, erlotinib and gefitinib, were characterized by significant dermatologic and gastrointestinal toxicities (2). One common mechanism of resistance to these first-generation EGFR inhibitors is the development of T790M mutations that change adenosine triphosphate affinity and result in steric hindrance of the inhibitors (3). Lung cancers with EGFR T790M mutations are not sensitive to the second-generation EGFR inhibitors afatinib and dacomitinib (4). For those reasons osimertinib was developed to overcome resistance to EGFR T790M mutations with minimal activity against the wild-type EGFR (4).

Osimertinib was originally approved by the Food and Drug Administration for patients who developed EGFR T790M mutations while on treatment with earlier generations of EGFR inhibitors (5). Subsequently, osimertinib was compared head-to-head with oral gefitinib or erlotinib in patients with treatment naive EGFR-mutated stage IIIB or IV NSCLC in the phase 3 clinical trial FLAURA (6). Osimertinib resulted in significant improvement in progression-free survival and overall survival over gefitinib or erlotinib (6,7). Also, because osimertinib can penetrate the central nervous system (CNS), the rates of progression of disease in the CNS were significantly lower in the osimertinib arm. Although there is some debate about the optimal sequence of targeted EGFR therapies, many oncologists use osimertinib for the frontline treatment of EGFR mutant NSCLC as per National Comprehensive Cancer Network guidelines (8).

EGFR is a receptor tyrosine kinase in the erythroblastic leukemia viral oncogene homolog (ErbB)/human epidermal growth factor receptor (HER) family that includes (human epidermal growth factor receptor 2) HER2. Antibodies that target HER2 like trastuzumab and small molecule inhibitors of HER2 like lapatinib have been approved for the treatment of HER2-amplified breast cancers. These agents have been associated with cardiotoxicity, especially in patients also receiving anthracyclines (9). The reported cardiotoxicity with these agents is often but not always reversible. HER2 is important in cardiac development and the maintenance of normal cardiac structure and function under stress conditions (9).

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Osimertinib also has modest activity against HER2, so it is not unanticipated that cardiotoxicity has been observed with this agent (4).

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In this issue of *JACC: CardioOncology*, Kunimasa et al. (10) report osimertinib-associated cardiac toxicity observed in a cohort of patients at the Osaka International Cancer Institute in Japan. Osimertinib-associated cardiotoxicity is relatively uncommon, yet an important issue in clinical practice. In this retrospective study, the electronic medical records of 123 patients with NSCLC and sensitizing EGFR mutations treated with osimertinib monotherapy between 2014 and 2019 were reviewed. Only 72 and 36 patients had baseline electrocardiograms or echocardiograms before osimertinib initiation, respectively. Six (4.9%) patients experienced grade ≥3 cardiac toxicity, which included acute myocardial infarction, heart failure with reduced left ventricular ejection fraction, and exacerbation of valvular heart disease. This study has many important findings that are important to clinical care. First, the frequency of cardiotoxicity reported in this study was higher than that reported in the original clinical trials with osimertinib. Similar findings have been reported with trastuzumab. It is not entirely surprising that adverse events are more common in the real-world setting than in restricted clinical trial populations (11,12). Second, patients can develop cardiac toxicity as early as 2 weeks on treatment, suggesting that cardiotoxicity may not represent a cumulative dose-dependent phenomenon. Third, this study suggested that patients who developed cardiac toxicity had a history of a cardiovascular disease or a risk factor for cardiovascular disease. In future prospective studies we may be able to validate this finding and ultimately predict which individuals are at high risk for untoward outcomes. Despite the limitations of this study, including the relatively small sample size and the lack of baseline and sequential electrocardiograms and echocardiograms at standardized time intervals, these findings may help guide future studies for identifying predictors of cardiotoxicity in patients with EGFR-mutant lung cancer treated with osimertinib.

Despite the concerns these results raise with osimertinib, they should be viewed in the context of the significant improvements in survival observed with osimertinib over prior generations of EGFR-targeting therapies and the CNS penetration of osimertinib, which improves the treatment of brain metastases, and the prevention of their development. For now, oncologists should counsel patients with cardiac disease or with multiple risk factors for such that there may be heightened risk for cardiotoxicity with this agent. Hopefully more sensitive predictors of cardiotoxicity will be discovered and incorporated into our clinical decision making.

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