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EDITORIAL COMMENT

Cardiac Risk-Informed Treatment of EGFR-Mutant Lung Cancer With Osimertinib*

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The oral epidermal growth factor receptor (EGFR) inhibitor osimertinib first received Food and Drug Administration (FDA) approval in November 2015 and has been widely prescribed by medical oncologists since that time, initially as a salvage therapy and over the past 18 months, as first-line treatment for patients with advanced EGFR-mutant non-small-cell lung cancer (NSCLC) (1,2). Osimertinib, like other EGFR tyrosine kinase inhibitors (TKIs), takes advantage of the unique cellular biology of a subset of NSCLCs. Defined by somatic mutations in the *EGFR* gene, this subset has an intracellular signaling network that is particularly dependent on the EGF receptor such that inhibition of EGFR leads to arrested cell growth and apoptosis producing profound and durable responses to EGFR TKI therapy, in contrast to the more modest responses that standard chemotherapies elicit.

Due to several potential advantages, osimertinib has become the preferred first-line therapy for *EGFR*-mutant cancers. A recent phase III randomized trial demonstrated improved duration of treatment efficacy (median length 19 months) and survival with osimertinib compared with older TKIs geftinib or erlotinib (3). Osimertinib also has a decreased incidence of common EGFR family side effects like rash and diarrhea, and better penetration into the brain (3,4). Yet, as treatment with osimertinib becomes more common, concerns have been raised regarding rare but potentially serious cardiac toxicities, which historically have not been reported with other EGFR TKIs. The study presented in this issue of *JACC: CardioOncology* by Anand et al. (5) represents the first large, systematic effort to quantify the risk of cardiac toxicities such as QTc prolongation and cardiac failure with osimertinib compared with other EGFR inhibitors.

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When considering cardiac toxicities of a treatment used in patients with lung cancer, the baseline risk of cardiac events must be taken into consideration. *EGFR*-mutant NSCLC is not associated with smoking; hence, most patients are remote or never smokers with low expected risk of cardiac events. In that setting, rare cardiotoxicities (heart failure and asymptomatic QTc prolongation) were noted even in the earliest phase 1 safety trial of osimertinib (6). Combined analysis of the first 2 randomized trials using osimertinib found an increased estimated pooled risk ratio of heart failure and QTc prolongation of 2.7 ($p = 0.03$) and 2.6 ($p = 0.003$), respectively, for osimertinib versus the comparator arms (7). Still, heart failure was rare, occurring in 21 (3.8%) of 558 patients treated with osimertinib in these 2 trials.

As part of the full FDA-approval process of osimertinib in 2017 (after conditional approval was granted in 2015), the FDA performed a risk/benefit analysis of osimertinib on a data set of 833 patients and noted 6 (0.7%) patients had developed a QTc >500 ms, 24 (2.9%) had an increase from baseline QTc >60 ms, and

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none had an associated arrhythmia (8). In addition, heart failure was observed in 16 (1.9%) patients and there was a single (0.1%) fatal event. With this low level of risk, the drug package insert was written to advise providers to monitor electrocardiograms and electrolytes in patients who have a history or predisposition for QTc prolongation, or those who are taking medications that are known to prolong the QTc interval, and conduct cardiac monitoring, including left ventricular ejection fraction assessment in patients with cardiac risk factors (9). Since that time, a real-world treatment study enrolled 3,015 patients treated with osimertinib for EGFR T790M-positive advanced NSCLC and reported 2% of patients developed QTc prolongation (none were serious); they did not assess for heart failure (10).

Although uncommon, cardiac toxicities have continued to be observed as the number of patients treated with osimertinib climbs. Case reports demonstrating serious outcomes have been reported, including fatal myocarditis (11), heart failure (12), and severe QTc prolongation attributable to osimertinib (13). The last of these cases highlights the therapeutic conundrum faced by oncologists encountering these rare but serious toxicities. After 11 months of osimertinib, a patient with a normal baseline QTc developed QTc prolongation to 560 ms. She was on no other QTc-prolonging drugs and a genetic screen for long-QT syndromes was negative. Osimertinib was held, but while awaiting a biopsy result to guide next steps, she developed cancer flare-up in the central nervous system related to being off osimertinib and died despite treatment with chemotherapy.

With this background, the analysis of the FDA Adverse Events Reporting System (FAERS) undertaken by Anand et al. (5) is timely and helpful. In this database, the total number of patients treated with each drug overall (denominator) is unknown, with emphasis instead on the number of reports of significant adverse events. The major downside of this database is that reporting is voluntary and likely does not encompass all events, introducing multiple forms of bias. In addition, the medical histories and circumstances of the toxicities are unknown. Nevertheless, the authors included data from FAERS encompassing 8,440 adverse events attributed to treatment with an EGFR TKI since January of 2016 and observed an overall low incidence of cardiac adverse events related to EGFR TKIs (n = 315). Still, among these, osimertinib was the culprit drug in approximately one-half of the cases (n = 158), whereas the 3 other EGFR TKIs queried (gefitinib, erlotinib, and afatinib) together shared responsibility for the other one-half of cardiac events (n = 157). In addition, the authors (5) calculated a reporting odds ratio by comparing rates of each adverse event associated with osimertinib to all other drugs in FAERS as well as to the 3 other EGFR TKIs, and found that the reporting odds ratio for osimertinib compared with all other drugs was 5.4 for cardiac failure and 11.2 for QTc prolongation, and compared with the 3 other EGFR TKIs was 2.2 for cardiac failure and 6.6 for QTc prolongation. In summary, this analysis confirms that as the number of patients treated with osimertinib is now likely in the tens or hundreds of thousands, a signal for rare and potentially serious cardiac events remains evident.

Although we agree with Anand et al. (5) that the risk of osimertinib cardiac toxicity should inform baseline testing and monitoring, the observed risks are not sufficient to warrant changes in prescribing of osimertinib. What remains most critical in our opinion is determining the best approach for baseline testing and on-treatment monitoring to allow identification of potentially serious toxicities early enough to intervene. For patients found to have an asymptomatic decrease in left ventricular ejection fraction, the appropriate frequency of monitoring and efficacy of dose-reduction remains unknown, while holding osimertinib can have dramatic negative consequences. For now, providers should be aware of osimertinib-induced cardiotoxicity and consider it in the differential for patients on this medication who are having shortness of breath, volume overload, palpitations, or other potentially relevant cardiovascular symptoms.

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