EDITORIAL

Perspective on the Cardiotoxicity of Third-Generation Targeted EGFRs in the Treatment of NSCLC

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Modern treatment for NSCLC is complex and at various stages can include surgery, radiation, cytotoxic chemotherapy, immunotherapy, and biological agents. These tumors constitute approximately 80% of all lung cancers. Notwithstanding considerable improvement in survival times, the outlook for patients with NSCLC remains suboptimal: a 2017 review on the basis of the Surveillance, Epidemiology, and End Results registry has revealed some improvement in survival rates, generally attributable to improvement in therapy and early diagnosis.[1] Nevertheless, the overall survival for these patients, once metastatic disease is present, remains low. Treatment strategies depend on stage at diagnosis, a variety of genetic tumor markers, previous therapies, and the condition and personal preferences of our patients.

Among the more recent additions to our therapeutic resources are the immune checkpoint inhibitors, often used sequentially with newer or more traditional chemotherapy, and third-generation targeted EGFR tyrosine kinase inhibitors (TKIs), of which osimertinib has received considerable attention.[2] Other EGFR agents have been approved by some agencies or are in advanced stages of clinical trials. These agents represent important progress in our battles against NSCLC. It is an exciting time regarding new drug development and a time when we can give some degree of tempered hope for a meaningful if limited prolongation of survival time for our patients with NSCLC.

TKIs have been followed by the specter of cardiotoxicity dating back to the first approval of these agents. Concerns were initially related to left ventricular dysfunction but subsequently expanded to include prolongation of the QT interval and related dysrhythmia. The mechanism of TKI-associated toxicities is uncertain and complex. With regard to myocardial contractility, the mechanisms are probably variable and multifactorial. Importantly, what has been observed is that the contractile dysfunction associated with TKIs is not universal and is not cumulative dose dependent, a factor that led to the following well-established categorization of cardiac dysfunction: type I is dose dependent and results in myocyte death, anthracycline being the poster child, and type II, not dose dependent, not related to primary cell death, and generally thought to be largely reversible. [3] With regard to osimertinib, the reported level of ejection fraction decrease in pooled data was 3.9%.[4] The reported events were mostly asymptomatic and resolved without treatment of the event or osimertinib discontinuation.

Furthermore, prolongation of the electrocardiographic QT interval has been associated with EGFR TKIs. Although the association is widely reported, confounding factors including other drug administrations and metabolic abnormalities may contribute to these events; anecdotal reports of torsades de pointes have been reported. In the report of the FLAURA trial, patients receiving osimertinib had a 10% incidence of QT prolongation, mostly grades 1 and 2, which is higher than in the standard EGFR TKI subset (4%).[2]

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In this issue of the *JTO Clinical and Research Reports*, we now have the interesting and timely report of cardiac events associated with a new third-generation EGFR TKI, lazertinib.[5] This new agent received approval in South Korea in January 2021, and wider approval and broader clinical use are anticipated. The report summarizes the cardiac events associated with lazertinib, and we found data highly suggestive of very low incidence of cardiac events. There is modest prolongation of the corrected QT interval in a small number of patients who were selected with an exclusion limit of the corrected QT interval of 470 msec. In addition, no troubling decreases in ejection fraction levels are found in their reported data.

A broad perspective of any form of drug-induced toxicity does not end with clinical trials. Surveillance during trials identifies and quantitates the instances of events that are specifically sought and finds other events if they are sufficiently common, even when unexpected. Events that are rare and unexpected or conditions that may not become apparent for long periods of time may come to the forefront only after considerable use and considerable time. It is for this reason that postmarketing surveillance and event reporting are so important. As the trial population may be different from that encountered in a real-world setting, and as the criteria and surveillance of events may be different as well, real-world data may be at variance and may trigger different conclusions. The present report does not include real-world cardiac event data for lazertinib, and thus it is premature to attempt a comparison of its incidence of cardiotoxicity with that of other agents. It will be of considerable interest to find if significant differences in cardiac events emerge among agents in this group.

The reported data are highly impressive, and the conclusion that "… lazertinib is not associated with increased cardiac risk" on the basis of the clinical trial data is justified, important, and inspires confidence on the question of cardiotoxicity for this agent. This conclusion, at least in spirit, is not at variance with the corresponding published conclusions regarding osimertinib, which also suggest a low risk of serious cardiotoxic events. Oncologists and their patients will have a choice of effective agents that are generally safe from the cardiac standpoint, but that have sufficient concern as to warrant some level of ongoing surveillance.

As for the oncologist, he or she will scrutinize the various agents that may be used in the treatment of the patient with NSCLC. They will look at response data as they emerge, and they will look at differences that are likely to affect the well-being of their patients, scrutinizing both clinical trial and real-world data. Formulary restrictions and cost considerations may also affect treatment decisions. It is hoped that future reports will confirm that serious cardiotoxicity events remain low and have limited impact for patients with NSCLC treated with these agents, allowing oncologists to focus on efficacy while not be overly concerned by low levels of cardiotoxicity as they select the most appropriate drugs from this category.

CRediT Authorship Contribution Statement

Michael S. Ewer: Writing—original draft.
Steven M. Ewer: Writing—review and editing.

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