Pathological assessment of osimertinib-associated cardiotoxicity in EGFR-mutated non-small cell lung cancer patients

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Background: Osimertinib, a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), inhibits both EGFR-TKI sensitizing mutations and resistant T790M mutations detected in non-small cell lung cancer (NSCLC) patients. Cardiac adverse events (AEs) induced by osimertinib are infrequent; however, cases of severe associated cardiac dysfunction have been reported and remain poorly understood.

Purpose: To assess pathogenesis of osimertinib-associated cardiac AEs, we analyzed myocardial specimens of three NSCLC cases with osimertinib-associated cardiac dysfunction.

Results: Analysis of LVEF prior to and after osimertinb administration in 36 NSCLC patients showed significant decrease of LVEF from 69% to 63%. Within this cohort, right ventricular (RV) biopsy was performed in 2 cases to further understand the pathophysiology of cardiac dysfunction. Case 1 was 78-year-old female with advanced NSCLC harboring an EGFR L858R mutation was treated with osimertinib as second line therapy. After 3 moths of osimetinib treatment, she presented with dyspnea, high NT-proBNP and troponin I, and significantly decreased left ventricular ejection fraction (LVEF) at 28%. RV biopsy showed moderate cardiomyocyte hypertrophy without inflammatory cell infiltration. Case 2 was 52-year-old female with advanced NSCLC harboring L858R mutation. She was treated with osimertinib as first line therapy. After 2 weeks of osimertinib, screening echocardiography revealed a reduction of LVEF from 63% to 41% without cardiac symptom. RV biopsy showed mild cardiomyocyte hypertrophy with infiltration of a few inflammatory cells in interstinum. We further analyzed death case of NSCLC. Case 3 was 63-year-old female with advanced NSCLC harboring EGFR ex. 19 del. and T790M mutations. After 6 months of osimertinib, she suffered from severe respiratory failure and severely reduced LVEF at 27%. She died on the 44th day after admission. Pathological autopsy revealed mild to moderate cardiomyocyte hypertrophy without inflammatory cell infiltration in both ventricles. These pathological findings may indicate neither myocyte injury nor myocarditis was induced by osimertinib in myocardium.

Conclusion: Although additional data collection of advanced NSCLC patients will be important in understanding the pathophysiology of cardiac AEs with osimertinib, osimertinib-associated cardiotoxicity may result from functional inhibition of myocyte contractility by osimertinib without induction of cell death or inflammation.