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HOW TO

How to Treat *EGFR*-Mutated Non–Small Cell Lung Cancer

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Mutations in the epidermal growth factor receptor (*EGFR*) gene are observed in about 15% of non-small cell lung cancer (NSCLC) adenocarcinomas in the United States compared to about 60% of NSCLC adenocarcinomas in Asia. These mutations are known to promote tumorigenesis and are seen predominantly in patients who are never-smokers, although they can also occur in patients with current or previous smoking history. There are multiple different mutations in the *EGFR* gene that confer varying levels of sensitivity to tyrosine kinase inhibitors (TKIs). The use of TKIs in the first-line setting became the standard of care after the IPASS (Iressa Pan-Asia Study) trial demonstrated that the oral TKI gefitinib improved progression-free survival compared to chemotherapy.[1] This foundational trial paved the path for the later-generation TKIs, including osimertinib. In this primer, we focus on the treatment of patients with the *EGFR* exon 19 deletion and exon 21 L858R mutations, which are the most common *EGFR* mutations.[2]

A lifelong never-smoker in her mid-50s with hypertension, premature ventricular contractions maintained on a beta-blocker, a remote history of resected renal cell carcinoma, and previous resected Stage IB *EGFR* exon 19 deletion adenocarcinoma of the right lower lobe presented 1 year into surveillance for the evaluation of 3 growing subcentimeter nodules, 1 of which was biopsy-proven recurrent *EGFR* exon 19 deletion lung adenocarcinoma. Brain magnetic resonance imaging (MRI) did not reveal any evidence of metastatic disease.

Molecular testing for "driver" mutations and alterations in NSCLC was historically performed with single-gene polymerase chain reaction and protein expression assays using immunohistochemistry on tumor samples. Now, this testing is standardly performed with next-generation sequencing platforms given the vast number of identified driver mutations and the improved sensitivity of this testing modality over single-gene polymerase chain reaction and immunohistochemistry. These next-generation sequencing platforms consist of multiplex testing of both tumor DNA and RNA. In addition, a blood-based "liquid biopsy," which has less sensitivity than tumor testing, can be sent with or in lieu of tumor sequencing to assist in detecting oncogenic "driver" mutations and fusions.

After a discussion with the patient about radiation to the growing nodules vs systemic therapy with the third-generation TKI osimertinib, she was started on osimertinib 80 mg once daily with subsequent radiographic improvement in the nodules. Despite the management of her acneiform rash with topical steroids and doxycycline, her osimertinib dose was decreased to 40 mg daily because of the ongoing acneiform rash and grade 2 transaminitis. About 9 months after starting osimertinib, she underwent screening echocardiography that detected a reduced left ventricular ejection fraction of 45% to 50%. She was asymptomatic and capable of routine exercise.

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HIGHLIGHTS

- Mutations in the *EGFR* gene are observed in about 15% of NSCLC adenocarcinomas in the United States and are not associated with smoking. There are numerous *EGFR* mutations, with the most common being exon 19 deletions and the point mutation L858R in exon 21.
- Osimertinib, an oral TKI, is used as the initial therapy for metastatic NSCLC harboring exon 19 deletion and exon 21 L858R mutation. Common side effects include acneiform rash, diarrhea, and paronychia. Osimertinib has also been associated with cardiomyopathy (~1.4%-2.4%) and prolongation of the QT interval (2.7%).
- In our experience, osimertinib-induced cardiomyopathy can be managed with the cessation of osimertinib and the initiation of guideline-directed therapy. Given that osimertinib is often the best available therapy, rechallenging with osimertinib often favors benefit over risk. Safe rechallenge with osimertinib is demonstrated in this case.

She was referred to cardio-oncology for further management.

Osimertinib, a third-generation TKI, has become the standard of care for first-line treatment of *EGFR*-mutated metastatic and recurrent lung cancer harboring *EGFR* mutations (exon 19 deletion and exon 21 L858R) based on the pivotal FLAURA (AZD9291 Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer) trial in which 80% of patients responded to treatment.[3] Also, compared with older TKIs such as erlotinib, osimertinib demonstrated an improved median overall survival (38.6 vs 31.8 months), an improved median progression-free survival (18.9 vs 10.2 months), and a 52% reduction in the risk of central nervous system progression. Unfortunately, resistance to osimertinib is inevitable, with a diverse cadre of resistance mechanisms implicated in osimertinib's loss of efficacy over time.[1]

In December 2020, osimertinib was approved for patients with Stage IB-IIIA resected *EGFR*-mutated lung cancer based on the ADAURA (AZD9291 Versus Placebo in Patients With Stage 1B-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy) trial, which randomized patients to observation vs 3-year treatment with adjuvant osimertinib. The ADAURA trial demonstrated a 24-month disease-free survival rate of 89% in the osimertinib group vs 52% in the placebo group (HR: 0.2).[4]

TKIs are associated with a unique side effect profile compared with traditional chemotherapy or immunotherapy. Common side effects of osimertinib include acneiform rash, paronychia/nail changes, diarrhea, and stomatitis. Osimertinib has also been associated with cardiomyopathy (~1.4%-2.4%), prolongation of the QT interval (2.7%), and interstitial lung disease (3.3%).[5]

In early trials of osimertinib, left ventricular ejection fraction was assessed at baseline and every 12 weeks thereafter until treatment discontinuation. The pooled rate of decrease in >10 percentage points from baseline to an absolute value of <50% observed in the FLAURA, AURA (AZD9291 First Time in Patients Ascending Dose Study), AURA extension, AURA2 (Phase II AZD9291 Open Label Study in NSCLC After Previous EGFR TKI Therapy in EGFR and T790M Mutation Positive Tumours), and AURA3 (AZD9291 [Osimertinib] Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer) studies was 3.9%.[6] Only 2% of patients in the AURA and AURA2 studies were codified with an adverse event of cardiac failure/cardiomyopathy, of which all of those attributed to osimertinib were grade 2 and below.[7] In the larger phase III FLAURA study of front-line osimertinib vs an early-generation TKI in untreated *EGFR*-mutated lung cancer, the adverse event cardiac failure was reported in 3.1% of osimertinib subjects compared with 1.2% in the comparator TKI group. Only 1 of 18 patients in these groups had TKI therapy discontinued because of cardiac failure, whereas 3 had treatment interrupted.

The FLAURA trial suggests a higher incidence of cardiac failure in osimertinib compared to earlier-generation TKIs. A review of "cardiac failure" in TKIs using the U.S. Food and Drug Administration Adverse Event Reporting System revealed a reporting OR of 5.4 (95% CI: 4.2-7.1) and 2.2 (95% CI: 1.5-3.2) for osimertinib compared to all drugs and older-generation TKIs, respectively.[8]

Repeat echocardiography 1 month later revealed a further reduction in her left ventricular ejection fraction to 35% to 40%. Electrocardiography demonstrated normal sinus rhythm. She was started on losartan. The patient's osimertinib treatment was discontinued. One week later, her treatment was

ABBREVIATIONS AND ACRONYMS

EGFR = epidermal growth factor receptor

NSCLC = non-small cell lung cancer

TKI = tyrosine kinase inhibitor

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AUGUST 2023:542–545

changed to erlotinib, a first-generation TKI. She underwent cardiac MRI about 1 month after discontinuing osimertinib, which revealed an improvement in her ejection fraction to 50%, as well as findings of microvascular disease of the left ventricle and diffuse fibrosis. Three- and six-month follow-up transthoracic echocardiograms revealed an improved ejection fraction to 50% to 55%, after which losartan and metoprolol were discontinued because of hypotension and positional dizziness.

Most side effects of osimertinib are managed with supportive care (eg, steroid cream for acneiform rash) or dose reduction; however, more serious side effects such as cardiomyopathy and pneumonitis are often managed with discontinuation of osimertinib. In addition, expert consensus suggests that cardiomyopathy can be managed with guideline-directed medical therapy, which includes renin-angiotensin system inhibition, beta-blockers, mineralocorticoid reception antagonists, and sodium-glucose cotransporter 2 inhibitors, as well as adjunctive therapies such as loop diuretics. There are few case series that report cardiac outcomes after the development of osimertinib-induced cardiomyopathy. In a cohort from a single center in Japan, 16 of 58 patients with a baseline and at least 1 on-treatment echocardiogram had developed a reduction of left ventricular ejection fraction of 10% or more after a mean of 6 months on osimertinib. Four of 5 patients who continued osimertinib had irreversible left ventricular ejection fraction reduction; none met cancer therapeutics-related dysfunction criteria (absolute decrease in left ventricular ejection fraction from baseline ≥10% to a value <53%). Discontinuation, dose reduction, or changing treatment to an alternative TKI resulted in recovery in 6 of the 8 patients meeting cancer therapeutics-related dysfunction criteria.[9] In a smaller case series of 3 patients, osimertinib was discontinued upon the development of cardiomyopathy, after which erlotinib was started in 2 patients after recovery of their ejection fraction without recrudescence. The other patient was rechallenged with osimertinib after his ejection fraction recovered, although the development of cardiomyopathy may have been related to tachycardia from atrial fibrillation rather than direct effects of osimertinib.[10] However, there is no consensus about whether patients who develop cardiomyopathy while on osimertinib can be subsequently rechallenged after recovery of their ejection fraction.

Although uncommon osimertinib has also been associated with prolongation of the QTc interval, most often with a change from baseline QTc, maintained at <500 milliseconds, although few grade III prolongations (QTc >501 milliseconds or an increase from baseline >60 milliseconds) have been reported. No QTc-related adverse clinical outcomes or cardiac failure were reported in clinical trials. Patients who start osimertinib should have electrocardiograms and electrolytes periodically monitored, particularly in patients predisposed to QTc prolongation or who are taking other medications that are known to prolong the QTc interval as QTc prolongation can be associated with arrhythmias and sudden cardiac death. Patients who develop QTc prolongation with evidence of life-threatening arrhythmias should permanently discontinue osimertinib. At this time, it is unknown if dose reduction is associated with a decreased risk of QTc prolongation.

Our patient developed disease progression in a cervical node and in multiple mediastinal nodes approximately 1.5 years after starting erlotinib. Her mediastinal nodes were rebiopsied with a bronchoscopy with endobronchial ultrasound and were found to still harbor an *EGFR* exon 19 deletion with no identifiable resistance mutation to osimertinib. Her brain MRI did not demonstrate metastatic disease. The decision was made to rechallenge her with osimertinib, but given her previous cardiomyopathy on osimertinib, she was started on 40 mg daily (the usual starting dose is 80 mg daily). Her metoprolol was continued, but neurohormonal therapy was not initiated given well-controlled blood pressures and previous low blood pressure and fatigue while on losartan. A repeat transthoracic echocardiogram obtained 6 weeks after restarting osimertinib demonstrated a preserved ejection fraction of 55%. Restaging positron emission tomography/computed tomography was obtained given the increased size of pulmonary nodules obtained on restaging chest computed tomography. There was an increase in metabolic activity and the size of a left lower lobe nodule; therefore, the patient's dose of osimertinib was increased to 80 mg daily. She was referred to radiation oncology and underwent 5 treatments of stereotactic body radiation therapy to the growing lung lesion. A transthoracic echocardiogram obtained about 8 weeks after her osimertinib was increased to 80 mg continued to show no changes to her ejection fraction. She remains on osimertinib 80 mg daily without any significant adverse effects.

The use of osimertinib in *EGFR*-mutant lung cancer represents an important milestone in the treatment of

mutation-driven lung cancer given its high response rates, central nervous system activity, and relative improvement of the duration of response compared to chemotherapy and previous TKIs. Given the increasing number of patients who will receive osimertinib in the adjuvant and metastatic setting, it is important for providers to be aware of osimertinib's unique side effect profile.

This case highlights the use of osimertinib in recurrent *EGFR*-mutated NSCLC, the development of cardiomyopathy, and the recovery of the ejection fraction with guideline-directed therapy and the use of a first-generation TKI after osimertinib toxicity. This case also demonstrates the potential for safe rechallenge with osimertinib despite a history of recovered osimertinib-induced cardiomyopathy.

Ultimately, the management of osimertinib-induced cardiomyopathy should be multidisciplinary and individualized to consider multiple factors, including the patient's baseline cardiac risk factors, degree of ejection fraction decrease, cardiac symptoms, mutational status (eg, T790M mutation is resistant to erlotinib), presence of central nervous system metastasis, next-best available therapy, and goals of therapy.

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