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Case Report

Osimertinib-induced Cardiac Dysfunction in EGFR-Mutated Lung Cancer: A Case Series of Five Patients

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Abstract

Introduction: The gold standard treatment for Epidermal Growth Factor Receptor (EGFR) positive Non-Small Cell Lung Cancer (NSCLC)patients is represented byosimertinib, an irreversible third-generation EGFR inhibitor that has been providingimportant outcomes' improvementscompared to chemotherapy and other target therapies; either upfront or as second line therapy, in case of EGFR T790M detection after previous tyrosine kinase inhibitors (TKI).Osimertinib is generally well tolerated. Most common side effects are diarrhea, rash, paronychia, dry skin and alsochanges in QT interval.

Presentation of case series: Here we report five cases of left ventricular dysfunction duringosimertinib treatment, observed between January 2017 and August 2018. The five patients, with a general low cardiovascular risk profile, required a dose modification/discontinuation of the TKI therapy and a specific cardio-protective treatment, normally with a recovery of the systolic function.

Conclusion: Both American and European compound labels highlight warnings of cardiomyopathy and changes in cardiac contractility during osimertinib treatment, recommending cardiac monitoring and dose adjustment in patients with cardiac risk factors. In spite of this, a standardized echocardiographic follow-up in the entire population is still not available and recommendations about the use of tissue Doppler echocardiography with more sophisticated indices are missing. With the expanding use of osimertinib we need better strategies to prevent or mitigate cardiovascular damage from cancer therapy in a larger multidisciplinary approach in which every issue is carefully evaluated.

Keywords: EGFR; lung cancer, osimertinib; cardiac toxicity; echocardiography

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Introduction

Treatment strategies for advanced NSCLC patients have rapidly evolved in recent years. Tumor molecular profilingled to the identification of genetic alterations, which drive and sustain tumorigenesis. Activating mutations in the EGFR kinase domain are the mostknown example of oncogenic drivers that can be therapeutically targeted by various small-molecule tyrosine kinase inhibitors (TKIs)[1]. In this patients' setting (10-15% of Caucasianpopulation),TKIs of both first (erlotinib and gefitinib) and second generation (afatinib) demonstrated significant advantages in terms of objective response rate (ORR), progression free survival (PFS) and quality of life (QoL), compared with standard platinum-based doublet chemotherapy [2-4]. Recently, another second generation TKI, dacomitinib, reporteda statistically significant and clinically meaningful improvement of overall survival (OS), compared to gefitinib, butlimited by more significant side effects[5].Despite markedly improved outcomes EGFR+ patients eventuallyexperience disease progression, typically within a year from treatmentbeginning.The most common mechanism of resistanceis the acquisition of T790M mutation within the EGFR kinase domainoccurring in approximately 60% of cases[6].Osimertinib, a third-generation EGFR TKI, targets bothEGFR activating and T790M resistance mutations.Based on thefavorable results from the phase II and phase III AURA trials [7,8],osimertinibreceived the approval for the treatment of EGFR T790M+ NSCLC who progressed during treatment with prior TKIs. Itsefficacy has been also reported in the front-line setting: in the FLAURA study the drug demonstrated a better PFS (18,9 vs 10,2 months) and ORR (80% vs 76%)with a lower toxicity compared to first generation EGFR TKIs[9]. Based on these resultsit has been approvedas a frontline treatment for patients with NSCLC who have tumors harboring EGFR mutations.

Osimertinib demonstrated a manageable toxicity profile. Most common adverse events (AEs)collected in first and further line trials (almost all grade 1 or 2) werediarrhoea, rash, dry skin and paronychia.In the FLAURA study,changes in QT interval (the majority of grade 1 or 2)represented the most common AEs in the cardiac category (29 patients, 10% in the osimertinib group vs 13 patients, 5%, in the standard EGFR-TKI group), and implied treatmentdiscontinuation or dosage reduction in 3% of patients.Other cardiac events, defined as"ejection fraction decrease" occurred in 8 patients (3%) in the osimertinib group and in 3 patients (1%) in the standard EGFR-TKI group and"cardiac failure"respectively in 12 patients (4%) and 6 patients (2%),determining dose interruptions in • 1% of patients (14).

Literature data available do not elucidatea clear causal relationship between cardiotoxicity and osimertinib. A consensus about the use of tissue Doppler echocardiography and more sophisticated indices (e.g. global longitudinal strain) for patients without cardiac risk factors is lacking; thus, collaboration betweenoncologists and cardiologists is strongly recommended. To date,two cases of congestive heart failure have been described only in Asiatic population[10,11].

Here, we report five cases of left ventricular dysfunction associated with osimertinib treatment observed between January 2017 and August 2018 (Figures 1-2).

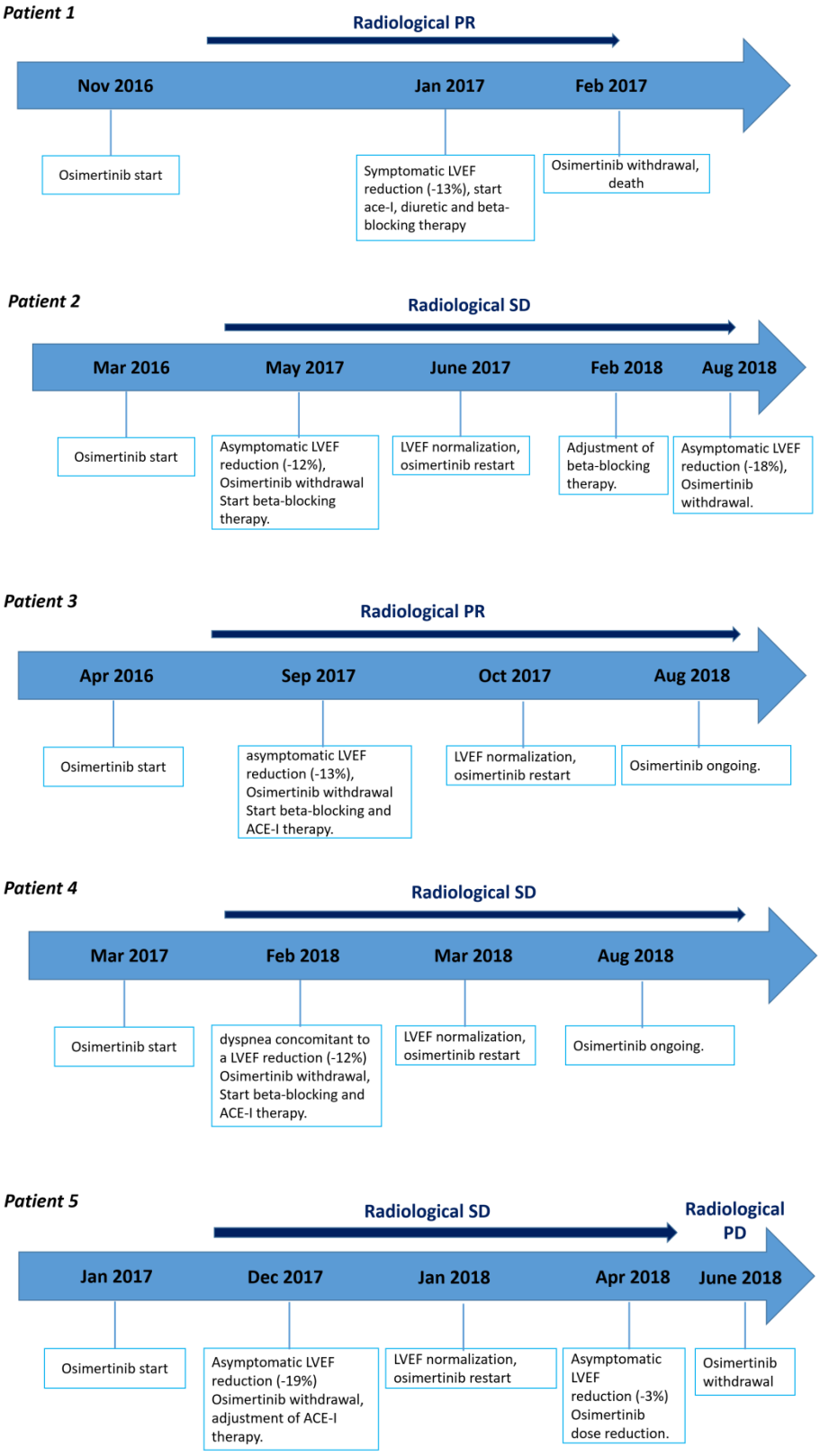

Figure1 Patients' clinical timelines: five cases of left ventricular dysfunction associated with osimertinib treatment

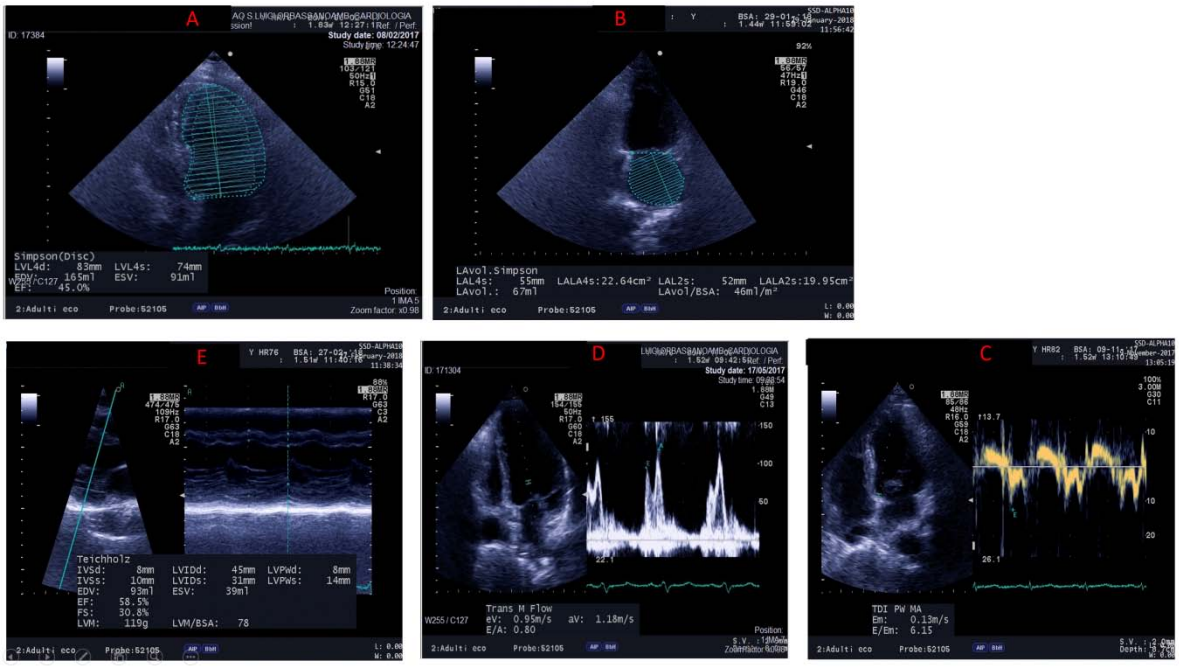

Figure.2 Main parameters collected during echocardiographic examination. A: left ventricular ejection fraction (EF)B: indexed left atrium end systolic volume indexed (LAVol/BSA). C: E prime wave on tissue Doppler echocardiography. D: E and A wave on trans-mitral pulsed Doppler. E: left ventricular M-mode misures in parasternal long axis view

Case presentations

PATIENT 1

A Seventy years-old former smoker men, was diagnosed with advanced stage EGFR-mutated (exon 19 deletion)lung adenocarcinomain January 2016. He received systemic treatment with gefitinib 250 mg/die with clinical benefit and radiological stable disease (SD) (byRECIST 1.1 Criteria). Due to radiologicaldisease progression and detectionof acquired resistanceT790M mutation on exon 20on a tissuebiopsy, the patient started osimertinib 80 mg/daily in November 2016 with a RECIST partial response (PR).Any cardiac comorbidityexcept from arterial hypertension was reported.

In October 2016 a baseline echocardiographic examshowed a normal left ventricle end-diastolic volume indexed on body surface area (LvVol D/BSA: 49 ml/m2) and a normal ejection fraction (EF: 60%). Left atrium end-systolic volume indexed on BSA (LAVol/BSA: 29 ml/m2) and diastolic function (E/A: 0,7; E/E': 9) were in range. Pulmonary artery pressure (PAPs: 30 mmHg) was normal.

In January 2017,despite a radiological stability of the disease, the patient progressively developed dyspnea. An echocardiographic re-evaluation was performed andrevealed a mild EF reduction (45%; -15% from baseline) without left ventricle dilatation, but with a moderate increase of left atrium volume (LAVol/BSA: 47 ml/m2). No increase in left ventricle filling pressure was found (E/A: 0,5; E/E': 6) sincethe patient had already started a diuretic therapy (furosemide 50mg twice daily);PAPs was 35 mmHG.Adequate medical treatment for cardiac failure was prescribed with low dose angiotensin converting enzyme inhibitor (ACEi), ramipril 2,5 mg, bisoprolol 1,25 mg daily and osimertinib was discontinued. Three weeks after drug withdrawal,a new echocardiographic

examination showed a substantial stability in EF (48%).Symptoms and clinical conditions progressively worsened, despite medical treatment and osimertinib withdrawal. To rule out ischemic events,a coronary artery CT scan was performed with theonly detection of a critical stenosis of the distal right coronary artery, deputed to supply only a small amount of myocardium. A diagnosis of osimertinib-induced cardiac toxicity was supposed and the heart failure therapy adjusted. Nevertheless,the patient died 10 days later, due to further worsening of cardiac condition.

PATIENT 2

A Seventy-three years-old never-smokerwomanwas diagnosed in October 2012 with stage IV, EGFR mutated (exon 19 deletion)NSCLC.After longradiological disease stability with gefitinib 250 mg/die, in March 2016 she developed T790M-induced acquired resistancedetected on tissue specimen (together with clinical and radiological lung progression) and started treatment with osimertinib 80mg/daily. The best radiological response during the 2nd line treatment was stable disease (SD). The patient reported a cardiologic history of intermittent left bundle branch block and arterial hypertension. The baseline echocardiographic evaluation showed a left ventricle volume at the upper reference limit (LvVol D/BSA: 61 ml/m2) with a small increase in indexed left ventricular mass (LVM/BSA: 104 gr/m2) and a normal systolic function (EF: 62%). A mild (2+/4) mitral valve insufficiency due to leaflets fibrosis was present. Left atrium volume (LAVol/BSA: 40 ml/m2) was enlarged, while the diastolic function (E/A: 0,7; E/E': 7) and the pulmonary artery pressure (PAPs: 30 mmHG) were normal. Along osimertinib treatment, the patient underwent regular echocardiographic controls every three months because of her cardiac history, without any pathological finding.

On May 2017, theroutine echocardiography showeda global left ventricular dysfunction (EF 50%, -12% from baseline). The indexed left atrial and left ventricular volumes remained stable.On the contrary, mitral valve insufficiency worsened becoming moderate (3+/4), together with an increase in filling pressure (E/A: 0,7, E/E': 14).

Even though the patient was asymptomatic, osimertinibwas suspended for 3 weeks and beta-blocker (bisoprolol1,25 mg per day) was administered. A new echocardiographic evaluation was performed in June 2017 demonstrating a recovery of left ventricle systolic function (EF: 62%). Thereafter,osimertinib was restartedat the same dosage. Monthly echocardiographic controlsshowed substantial EF stability (62% → 63% → 58% → 61%) and a progressive diastolic function improvement (E/A: 0,8 → 2,2 → 1 → 0,6; E/E': 18 → 12 → 9 → 7). Due to a new reduction in EF (61% →54%) and enlargement of left ventricular volume (LvVol D/BSA: 80 ml/mq), without any symptoms, in February 2018 the bisoprolol was up-titrated at 3,75 mg per day and osimertinib suspended. Subsequent echocardiographic controls demonstrated a small EF improvement (58%) with a substantial stability of other parameters. In August 2018 due to a new reduction of EF (40%)osimertinib was temporary suspended. Echocardiographic monitoring is ongoing to evaluate the treatment strategy.

PATIENT 3

A Forty-seven years-old never-smoker woman was diagnosed in January 2012 with stage IV NSCLC, EGFR mutated (exon 19deletion). In April 2016 osimertinib 80 mg/daily was undertaken for lung progression togefitinib 250 mg/die (T790M+ detection on tissue). The best radiological response during the 2nd line treatment was PR.

The baseline echocardiographic evaluation did not show any pathological finding. The first echocardiogram, performed six months after osimertinib therapy starts, showed normal dimensions

(LAVol/BSA: 27ml/m2; LvVol D/BSA: 54 ml/m2) and function (EF: 64%; E/A: 0,8; E/E': 6) of the left cardiac chambers. Two further echocardiograms, performed at nine and twelve months, confirmed these findings. In September 2017,osimertinib was suspended due to asymptomatic LVEF (left ventricular ejection fraction) reduction (EF 51%, -13% from baseline).Left chamber volumes and diastolic function were not affected from this systolic function reduction. Under cardiologic consultation, therapy with bisoprolol (5 mg/day) and perindopril (5 mg/day) was administered, resulting in a partial recovery of cardiac function (EF: 56%, + 5%), and osimertinib restarted (October 2017).Close echocardiographic monitoringcontinued and the patient underwent a full recovery of the systolic function (EF: 60%).

PATIENT 4

A Seventy-oneyears-old never-smoker woman was diagnosed in April 2015 with stage IV NSCLCEGFR mutated (exon 19 deletion). Due to lung disease progression to gefitinib 250 mg/die and T790M detection on tissue, the patient started osimertinib 80 mg/daily in March 2017. The best radiological response during the 2nd line treatment was SD.

The baseline echocardiographic evaluation showed normal dimensions (LAVol/BSA: 24 ml/m2; LvVol D/BSA: 55 ml/m2) and function (EF: 58%; E/A: 0,6; E/E': 4) of the left cardiac chambers. Echocardiograms performed in the following eleven months were stable, except for the presence of a mild, stable, circumferential pericardial effusion. In February 2018, osimertinib was suspended due to dyspnea associated with a LVEF reduction (EF 45%, -12% from baseline). Left ventricle and left atrium volumes were both mild dilated (LAVol/BSA: 42 ml/m2; LVVol D/BSA: 83 ml/m2).The cardiologic consultation led to the introduction of bisoprolol 2,5 mg/daily, furosemide 12,5 mg/daily and perindopril 2,5 mg/daily: a subsequent partial recovery of cardiac function (EF: 54%, + 8%) was observed together with the left chambers volume reduction (LAVol/BSA: 40 ml/m2; LVVol D/BSA: 70 ml/m2) andregression of dyspnea. Fifteen days after interruption,osimertinib therapy was resumed along with cardiologic therapy prosecution. Clinical and echocardiographic controls showed a stabilization of the cardiac function.

PATIENT 5

A Eighty years-old never-smokerwoman affectedby stage IV EGFR mutated (exon 19 deletion)NSCLC(diagnosis in October 2014) started a first line therapy with gefitinib 250 mg/die; in January 2017 because of lung progression and detection of T790M mutation on plasma, the treatment withosimertinib 80 mg/daily was started.The best radiological response during the 2nd line treatment was SD. Arterial hypertension was the only patient's comorbidity. The baseline echocardiographic evaluation did not show any pathological findings. The first echocardiogram performed two months later showed a mild enlargement of the left atrium (LAVol/BSA: 35 ml/m2), a mild increase in indexed left ventricular mass (LVM/BSA: 97 gr/m2)and normal dimensions (LvVol D/BSA: 61 ml/m2) and function (EF: 62%; E/A: 0,5; E/E': 5) of the left ventricle.After eleven months of therapy the patient developed an asymptomatic reduction of the systolic function (EF: 43%, -19% from baseline) and an increase in left ventricle mass and left atrial volume (LVM/BSA: 104 gr/m2; LAVol/BSA: 50 ml/m2). Osimertinib was temporarily suspended and enalapril therapy titrated from 2,5 mg to 5 mg per day. Three weeks after osimertinibdiscontinuation, a new echocardiogram showed a systolic function improvement (EF 43% → 55%) and stabilization of left chambers volumes, thuswe reintroduced the target therapy. In April 2018 themonthly cardiac follow updemonstrated further reductionin systolic

function (EF 52%). We reducedosimertinib dose at 40mg/die with a stable echocardiographic monitoring until June 2018 when the treatment was permanently discontinued for progressive disease.

Discussion

American and Europeanosimertinib labels both carry warnings of cardiomyopathy and changes in cardiac contractility during treatmentand recommendcardiac monitoring (assessment of LVEF at baseline and during treatment) in patients with cardiac risk factors or with conditions that can affect LVEF. A dose modification/discontinuation is suggested in case of decrease in LVEF of 10% from baseline and below 50%, or in case of symptomatic congestive heart failure[12]. A causal underpinning of relationship between osimertinib and cardiaccomplications remains weak. Actually, many of the pathways responsible for proliferation in malignant cells also play crucialroles in cardiomyocytes biology, such as survival and electrical and contractile function. Implications of tyrosine kinases in cardiomyocyte survival signaling were first evaluated with trastuzumab (a monoclonal antibody against human epidermal growth factor receptor 2). Another EGFR family member, ERBB1, inhibited by osimertinib, may also be involved in cardio protectionand myocyte survival, based on common downstream pathways to the EGFR family receptors[13]. Our case series confirms the potential risk of osimertinib-related cardiac toxicity and allows some hypotheses:

1. Cardiac toxicity seems only partially related to previous cardiac conditions or high cardiovascular profile risk. With the exception of one patient,bearinga moderate valvular disease, none of our patients had previous cardiovascular diseases and their cardiovascular risk profile was low, as in the other two clinical cases already reported [10, 11].
2. Osimertinib cardiac toxicity seems to be more common in female (as in the two previous case reports and in four of our five patients). We can partly explainthis observation with the highest prevalence of NSCLC with EGFR mutation in females.However, a gender difference influencecould not be excluded [14].
3. Osimertinib cardiotoxicity seems to be reversible and, for this reason, is more likely to be a type 2 cardiotoxicity, like the trastuzumab-related one. Similarly to previous observations made on trastuzumab treated patients, we did not find a worsening of diastolic function, but only a systolic function impairment. Then, type 2 cardiotoxicity could have a different behavior than type 1, in which the systolic function is affected after the development of a diastolic dysfunction[15].We underline, however, the very small sample size upon which this hypothesis is based.
4. The development of protocols including global longitudinal strain (GLS) and cardiac magnetic resonance is, in our opinion, of paramount importance to identify patients who could benefit of a dosage reduction or a transitory interruption of osimertinib in order to prevent the progression to an overt cardiac dysfunction.
5. The use of beta-blockers and ACEi seems to have a sort of cardio-protective role in patients who develop a reduction of systolic function[16]. This topic needs further investigationsin order to determine whether continuingosimertinib in association with a cardioprotective therapy in patients who develop an initial cardiac dysfunctionis safe or not.

Conclusions

In this scenario of paramount efficacy and a global favorable safety profile ofosimertinib, a rising awareness of cardiovascular complications can help the minimization of adverse toxicities. A fully understanding of the risk factors plays a critical role. Prospective data investigating the role of routine

high sensitivity troponin evaluation, brain natriuretic peptide(BNP), tissue Doppler and speckle tracking echocardiography could representtools to early identify cardiac toxicity. With the expanding use of osimertinib, even in front-line setting, we should keep in mind that strategies to prevent or mitigate cardiovascular damage from cancer therapies are important to provide the best care. Cancer treatmentsare multifaceted and need not only the well-known coordination among oncologists, surgeons and radiation oncologists but also a larger multidisciplinary approach in which every issues, including potential toxic side effects,are carefully evaluated.

Consent

The patients/families have given their informed consent for the case series to be published.

References

1. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. ***Science***. 2004, 304:1497-1500
2. Mitsudomi T, Morita S, Yatabe Y, et al. West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non–small cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. ***Lancet Oncol***. 2010, 11:121-128
3. Rosell R, Carcereny E, Gervais R, et al; Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation–positive non–small cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. ***Lancet Oncol***. 2012, 13:239-246
4. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. ***J ClinOncol***. 2013, 31:3327-3334
5. Mok TS, Cheng Y, Zhou X, et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. ***J ClinOncol***. 2018, 36(22):2244-2250.
6. Lovly CM, Shaw AT. Molecular pathways: resistance to kinase inhibitors and implications for therapeutic strategies. ***Clin Cancer Res***. 2014, 20:2249-2256.
7. Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. ***Lancet Oncol***. 2016, 17(12):1643-1652.
8. Mok TS, Wu YL, Ahn MJ, et al. AURA3 Investigators. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. ***N Engl J Med***. 2017, 376:629-640.
9. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. ***N Engl J Med***. 2018, 378:113-125
10. Watanabe H, Ichihara E, Kano H, et al. Congestive Heart Failure DuringOsimertinib Treatment for Epidermal Growth Factor Receptor (EGFR)-mutant Non-small Cell Lung Cancer (NSCLC). ***InternMed***. 2017, 56(16):2195-2197
11. Oyakawa T, Nakashima K, Naito T. Cardiac Dysfunction Caused by Osimertinib. ***J ThoracOncol***. 2017, 12(10):e159-e160

12. AstraZeneca. Tagrisso™ (osimertinib) tablets, for oral use: US prescribing information. 2017. http://www.fda.gov/. Accessed 24 March 2018.
13. Reichelt ME, O'Brien S, Thomas WG, et al. Transactivation of the epidermal growth factor receptor in responses to myocardial stress and cardioprotection. ***Int J Biochem Cell Biol***. 2017, 83:97-110
14. Ben Aissa A, Mach N. Is lung cancer in women different?. ***Rev Med Suisse***. 2012, 8(342):1108-1111.
15. Honda K, Takeshita K, Murotani K, et al. Assessment of left ventricular diastolic function during trastuzumab treatment in patients with HER2-positive breast cancer. ***Breast Cancer***. 2016, 24: 312-318
16. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. ***J ClinOncol***. 2005, 23(13):2900-2902