Posted on Authorea 12 May 2022 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.165237524.41129461/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Reoccurence of Takotsubo Cardiomyopathy Induced by Osimertinib: Case Report

Yuko Fukuda[1], Yoshitaka Kawa[1], Akiko Nonaka[1], and Hideyuki Shiotani[2]

[1]Hyogo Cancer Center
[2]Kobe Tokiwa University

May 12, 2022

Abstract

A patient with lung cancer was administrated osimertinib. She developed symptomatic heart failure due to Takotsubo-cardiomyopathy (TC). As her condition improved after discontinuing osimertinib, TC was thought to be caused by osimertinib. Re-occurrence of TC was seen after re-administraing half dose of osimernitib.

Reoccurence of Takotsubo Cardiomyopathy Induced by Osimertinib: Case Report

[1]Yuko Fukuda, MD, PhD, [2]Yoshitaka Kawa, MD, PhD, [1]Akiko Nonaka, MD, PhD,[3]Hideyuki Shiotani, MD, PhD

[1]Division of Onco-cardiology, Hyogo cancer center,[2]Division of Respiratory Medicine, Hyogo cancer center, [3]Division of Health Sciences,Department of Nursing, Kobe Tokiwa University

Corresponding Author

Yuko Fukuda, MD, PhD

Division of Onco-cardiology, Hyogo cancer center, Akashi, Japan

13-70, Kitaoji-cho, Akashi, 673-8558, Japan

Tel; +81-78-929-1151, Fax; +81-78-929-2380

E-mail; yukoishikawa3825@yahoo.co.jp

ORCID iD: 0000-0001-9199-0246

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Word count for the manuscript : 1272 words

Number of table: 1

Number of figures: 2

Keywords: osimertinib, heart failure, Takotsubo cardiomyopathy, stress cardiomyopathy

Introduction

Chemotherapy-induced Takotsubo (stress) cardiomyopathy (TC) have been reported for several anticancer agents including antimetabolites, fluoropyrimidines, and molecularly targeted agents(1). Some molecularly

Posted on Authorea 12 May 2022 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.165237524.41129461/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

targeted agents reportedly cause cardiovascular side effects, including heart failure, arrhythmia (QT prolongation), and myocardial infarction (2). The epidermal growth factor receptor (EGFR) inhibitors except trastuzumab are known to cause less cardiotoxicity than BCR-ABL inhibitors and vascular endothelial growth factor (VEGFR) inhibitors (3). However, osimertinib has been reported more adverse cardiac events than other EGFR inhibitors, including heart failure (4-6). While there exist a few reports of osimertinib-induced heart failure in detail, none have so far reported TC induced by osimertinib. Herein, we report a case of TC caused by osimertinib.

Case History

A 73-year-old woman with no history of smoking underwent a thoracoscopic right upper-middle lobectomy in 2016 for non-small cell lung cancer (NSCLC). Her clinical stage was T2N0M0, and she did not receive adjuvant chemotherapy. One year later, a chest computed tomography (CT) scan showed pleural dissemination, and brain metastasis was suspected based on brain magnetic resonance imaging (MRI). She was admitted to our institution for targeted therapy. One year and 10 months after administering erlotinib and bevacizumab as first-line therapy (a total of 26 courses), pleural dissemination was found to be a progressive disease. Pleural biopsy revealed a T790M mutation.

Osimertinib (80 mg/day, taken orally) was chosen as the second-line therapy. Within one month of starting osimertinib, she was admitted to our institution with progressive shortness of breath, fatigue, and edema in the body and extremities. Chest radiography revealed pulmonary congestion, pleural effusion, and cardiac dilation. An echocardiogram revealed left ventricular akinesis from the apical to the midventricular portion, which did not match with coronary arterial perfusion (Fig 1(A, B)). The left ventricular dimension increased from 34 mm pre-osimertinib treatment to 46 mm, and left ventricular ejection fraction (LVEF) was reduced from 75% to 58%. The eletrcocardiogram changed from normal to a right bundle branch block (Fig 2(A, B). She was diagnosed as symptomatic acute heart failure.

Differential Diagnosis

The differential diagnosis of cause of heart failure included coronary artery disease, arrhythmia, and valvular disease. Cardiac MRI showed no significant stenosis of the coronary arteries, and a monitored electrocardiogram showed no bradycardia nor tachycardiac arrhythmia. Echocardiography revealed no significant left-side valvular disease.

Outcome and Follow-up

She was diagnosed with osimertinib-induced acute heart failure due to TC. She was admitted to our institution on the same day for treatment of cardiac failure. Her condition improved after discontinuing osimertinib and adding treatment for heart failure.

Thirty-five days after admission, left ventricular wall motion abnormality improved to almost normal kinesis (Fig 1(C, D)), and electrocardiogram showed ST changes normalized after extensive negative T waves (Fig 2(C, D)). She improved from class IV to class II as per the New York Heart Association classification.

Since osimertinib was highly effective against lung cancer, the treatment was restarted at a reduced dose of 40 mg/day. After 63 days of restarted osimertinib therapy, an echocardiogram showed hypokinesis on the left ventricular apical portion (Fig 1(E, F)). Electrocardiogram showed reappearance of extensive negative T waves (Fig 2(E)). She was diagnosed with asymptomatic TC, and osimertinib treatment was subsequently stopped. Two weeks after stopping osimertinib, left ventricular wall motion improved to normal. She was started on 3rd-line chemotherapy.

Discussion

Osimertinib is a third-generation oral EGFR tyrosine kinase inhibitor (TKI) used for the treatment of advanced EGFR-mutant NSCLC with acquired T790M mutations. It has also been shown to improve progression-free survival compared to platinum therapy (7). Although cardiotoxicity from EGFR-TKI (hu-

Posted on Authorea 12 May 2022 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.165237524.41129461/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

man EGFR1: HER1) has been reported to be less than that of HER2, BCR-ABL, and VEGFR inhibitors (3), osimertinib is likely to cause cardiac side effects (4-6).

TC is a transient systolic left ventricular dysfunction with a variety of wall motion abnormalities (8). Elderly women and emotional or physical triggers were considered to be the cause of TC, but conditions without an evident trigger have also been reported (8,9). In a previous study, EGFR was found to be expressed in the central nervous system, and infusion of EGFR into the midbrain had increased dopamine precursor levels in an experimental rat model. One of the mechanisms of osimertinib-induced TC might be that osimertinib, may cross the blood-brain barrier, increasing the dopamine release in the central nervous system (10).

Osimertinib may cause TC, which has the possibility of cause of heart failure. The findings of our case study suggest that osimertinib therapy should not be resumed in patients diagnosed with symptomatic heart failure due to TC induced by osimertinib.

Authorship Contributions:

All authors made substantial contributions to prepare and writing the manuscript, and were involved in revising it critically for important intellectual content, and gave final approval of the version for submission.

Conflict of Interest

None declared.

References

1. Smith SA, Auseon AJ. Chemotherapy-induced takotsubo cardiomyopathy. Heart Fail Clin 2013;9:233-42, x.

2. Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. Acta Oncol 2009;48:964-70.

3. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer 2007;7:332-44.

4. Anand K, Ensor J, Trachtenberg B, Bernicker EH. Osimertinib-Induced Cardiotoxicity. JACC: CardioOncology 2019;1:172-178.

5. Kunimasa K, Oka T, Hara S et al. Osimertinib is associated with reversible and dose-independent cancer therapy-related cardiac dysfunction. Lung Cancer 2021;153:186-192.

6. Kunimasa K, Kamada R, Oka T et al. Cardiac Adverse Events in EGFR-Mutated Non-Small Cell Lung Cancer Treated With Osimertinib. JACC CardioOncol 2020;2:1-10.

7. Hirashima T, Satouchi M, Hida T et al. Osimertinib for Japanese patients with T790M-positive advanced non-small-cell lung cancer: A pooled subgroup analysis. Cancer Sci 2019;110:2884-2893.

8. Medina de Chazal H, Del Buono MG, Keyser-Marcus L et al. Stress Cardiomyopathy Diagnosis and Treatment: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:1955-1971.

9. Templin C, Ghadri JR, Diekmann J et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med 2015;373:929-38.

10. Iwakura Y, Nawa H. ErbB1-4-dependent EGF/neuregulin signals and their cross talk in the central nervous system: pathological implications in schizophrenia and Parkinson's disease. Front Cell Neurosci 2013;7:4.

Table Legend

Echocardiographic parameters, BNP values and Number of Figure of echocardiogram and electrocardiogram from baseline to TC treatment.

Posted on Authorea 12 May 2022 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.165237524.41129461/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

AHF: acute heart failure, TC: takotsubo (stress) cardiomyopathy, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, FS: fractional shortening, LVEF: left ventricular ejection fraction, TR: tricuspid regurgitation, PG: pressure gradient, GLS: global longitudinal strain using speckle tracking method

Figure Legends

Figure 1 : Echocardiography on acute heart failure due to TC (A: diastole, B: systole), after treatment of heart failure (C: diastole, D: systole), and on reoccurrence of TC (E: diastole, F: systole)

Fig 1(A, B). Akinetic left ventricle wall motion is seen from the apical to mid portion (yellow arrows on Fig(B)), which does not match with the coronary arterial perfusion. Basal wall motion is hyperkinetic instead.

Fig 1(C, D). Thirty-five days after treatment of heart failure. Left ventricle wall motion improved to almost normal kinesis.

Fig 1(E, F). Sixty-three days after restarting osimertinib, akinetic left ventricle wall motion on apical portion was seen (yellow arrows on Fig(F)).

Figure 2: Electrocardiogram on baseline (A), on acute heart failure (B), after heart failure treatment (C, D), and on reoccurrence of TC (E).

Fig 2(A). Baseline electrocardiogram was normal sinus rhythm with heart rate of 71bpm.

Fig 2(B). On acute heart failure due to TC, an electrocardiogram showed complete right bundle branch block with heart rate of 92bpm.

Fig 2(C). Eleven days after treatment of heart failure. Negative T-wave with broad induction was observed.

Fig 2(D). Nine weeks after treatment of heart failure. ST changes has normalized.

Fig 2(E). Sixty-three days after restarting osimertinib. Negative T-wave with broad induction was observed.

Hosted file

`Figure TC 20220506.docx` available at https://authorea.com/users/482268/articles/568873-reoccurence-of-takotsubo-cardiomyopathy-induced-by-osimertinib-case-report

Hosted file

`Table 20220502.docx` available at https://authorea.com/users/482268/articles/568873-reoccurence-of-takotsubo-cardiomyopathy-induced-by-osimertinib-case-report