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**Case Report**

# Successful Rechallenge with Osimertinib following Osimertinib-Induced Ventricular Tachycardia: A Case Report

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**Keywords**
Cardiotoxicity · Lung cancer · Osimertinib · Ventricular tachycardia

**Abstract**
Osimertinib, a third-generation tyrosine kinase inhibitor, is the first-line treatment for metastatic non-small cell lung cancer (NSCLC) with sensitizing epidermal growth factor receptor (EGFR) mutations. It is known to cause drug-induced cardiotoxicity, including QT prolongation syndrome, heart failure, and ventricular arrhythmias, which can lead to sudden death. Once severe arrhythmias occur, it is difficult to continue osimertinib treatment. We report a case of a 66-year-old woman with recurrent NSCLC after concurrent chemoradiotherapy who experienced osimertinib-induced ventricular arrhythmia-causing syncope. The patient was initially treated with concurrent chemoradiotherapy, and genetic testing revealed EGFR exon 19 deletion. Three years following treatment initiation, the primary tumor progressed, and new bone metastases developed. The patient was diagnosed with recurrent NSCLC and was treated with targeted therapy with osimertinib. On the 10th day of osimertinib administration, syncope occurred. Electrocardiography showed polymorphic non-sustained ventricular tachycardia, which was believed to be the cause of syncope. The patient was switched to erlotinib. Two and a half years later, disease progression in the primary lesion was observed. A liquid biopsy revealed an EGFR T790M resistance mutation. Therefore, osimertinib (40 mg) was administered every alternate day. After confirming the absence of palpitations and arrhythmias on electrocardiogram, the osimertinib dosing was increased to 40 mg daily. Thereafter, no further events occurred, and tumor shrinkage was observed. Low-dose osimertinib rechallenge after induced ventricular arrhythmia may be considered an option under close monitoring; however, osimertinib rechallenge must be carefully selected based on the risk-benefit analysis.



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## Introduction

Targeted therapies have significantly enhanced the prognosis of patients suffering from non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), selectively inhibits both EGFR-TKI-sensitizing mutations and EGFR T790M resistance mutations [1]. Osimertinib is generally well tolerated; however, prevalent adverse reactions comprise diarrhea, rash, and dry skin. Notwithstanding, a rare yet possibly fatal complication is cardiotoxicity, which occurs in 9.9% of patients [2–6]. According to a retrospective study based on data from 2016–2018 in the USA, osimertinib significantly increased the risk of cardiotoxicity, including cardiac failure, atrial fibrillation, QT prolongation, myocardial infarction, and pericardial effusion, compared to other EGFR-TKIs [7]. Previous reports have shown QT prolongation and ventricular fibrillation in patients with lung cancer treated with osimertinib [8, 9].

There are several reports of successful rechallenge with osimertinib after osimertinib-induced pneumonitis [10, 11]; however, there have been few reports of successful rechallenge after osimertinib-induced cardiotoxicity [12]. Here, we describe a case of successful rechallenge with osimertinib after induced ventricular arrhythmia with syncope. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533826).

## Case Presentation

A 66-year-old Japanese woman presented with a lung nodule in the left lower lobe. She was a nonsmoker, with no history of exposure to passive smoking, underlying cardiac disease, or family history of sudden cardiac death. Serum carcinoembryonic antigen (CEA) level was 11.4 ng/mL. She was diagnosed with lung adenocarcinoma based on computed tomography-guided transthoracic biopsy and was positive for the EGFR exon 19 deletion mutation. Fluorodeoxyglucose positron emission tomography revealed a 2-cm nodule in the lower lobe of the left lung and lymph nodes in the subcarinal area. Contrast-enhanced magnetic resonance imaging of the head revealed no brain metastases. Based on these results, we clinically staged the lung cancer as T2aN2M0 stage IIIA. She was initially treated with concurrent chemoradiotherapy (carboplatin [area under the curve, 2, weekly], paclitaxel [40 mg/m$^2$, weekly], and thoracic radiation 60 Gy/30 fractions). Following 3 years of progression-free survival, the patient developed progressive primary lung adenocarcinoma and bone metastasis. Due to lung adenocarcinoma recurrence, osimertinib (standard dose of 80 mg per day) was administered based on molecular gene profiling. Pretreatment electrocardiogram (ECG) showed sinus rhythm (heart rate, 99 bpm) and no ventricular arrhythmia. On the 10th day of therapy, the patient experienced syncope while climbing the stairs and was transported by ambulance to the emergency room of a nearby hospital. She was unaware of any chest symptoms prior to the syncope episode. At that time, no medications other than anticancer drugs had been prescribed. Laboratory workup revealed a white blood cell count of 8,100/μL, hemoglobin of 12.6 g/dL, platelet count of 168,000/μL, c-reactive protein level of 0.19 mg/dL, creatine kinase of 72 IU/L, creatine kinase isoenzyme (MB) at 4.4 ng/mL, Na 141 mEq/L, K 3.5 mEq/L, Cl 103 mEq/L, thyroid-stimulating hormone at 2.177 μIU/mL, free thyroxine at 1.09 ng/mL, and troponin T level of 0.03 ng/mL. An ECG showed sinus tachycardia (100 bpm), ventricular bigeminy, and no QT prolongation (QTc, 419 ms) (Fig. 1). Five days after the incident, the patient visited our hospital with no other symptoms. Ultrasonic cardiography

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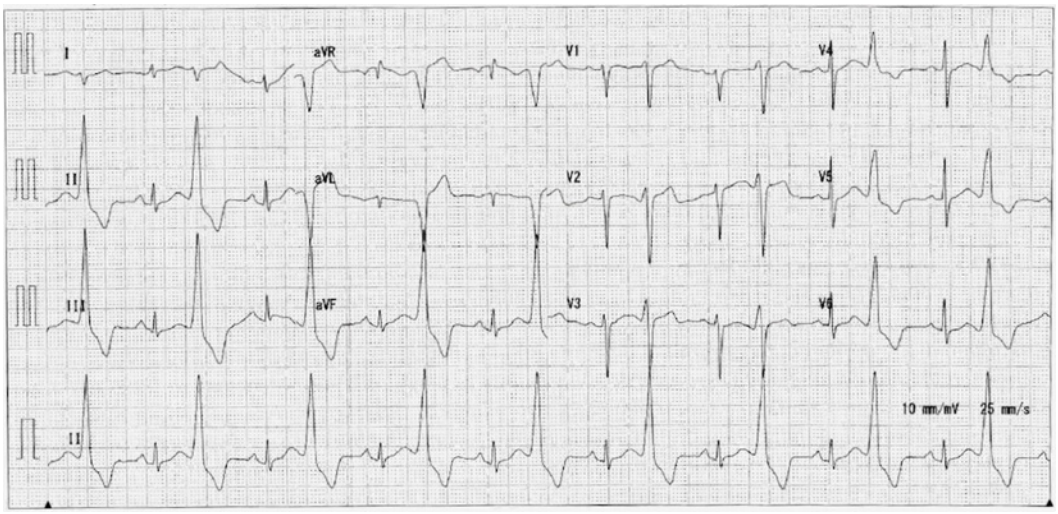


**Fig. 1.** ECG at the time of emergency transport exhibiting sinus tachycardia (heart rate: 100 bpm) and ventricular bigeminy but no QT prolongation (QTc 419 ms).

revealed no evidence of structural or functional cardiac abnormalities. A 24-h Holter ECG was recorded, with a mean heart rate of 104 bpm (range, 86–135 bpm) in sinus rhythm and a total heart rate of 148,701 beats. Of these, 55,216 (37.1%) polymorphic ventricular complexes were identified, including 59 ventricular extrasystole events and two non-sustained ventricular tachycardias (NSVTs) (Fig. 2). As we could not identify any causes other than osimertinib (e.g., electrolyte abnormalities or suspicious drugs), we considered NSVT with syncope induced by osimertinib. We discontinued osimertinib and started an oral β-blocker. After 3 weeks, ECG revealed sinus rhythm (heart rate, 75 bpm) and no ventricular arrhythmia. Osimertinib was shifted to erlotinib at 150 mg per day. The dose was reduced temporarily to 100 mg due to a grade 2 acneiform rash; however, erlotinib had achieved a partial response for about two and a half years, and serum CEA decreased to 4.1 ng/mL.

CT and PET revealed progression of the primary lung lesion, and the serum CEA level was elevated to 56.8 ng/mL. Liquid biopsy (cobas® EGFR Mutation Test ver. 2, Roche, Basel, SW, USA) confirmed the presence of EGFR exon 19 deletion and T790M mutation, which is a common resistance mutation to erlotinib. Full informed consent was obtained from the patient regarding the risk of recurrent syncope with ventricular arrhythmia, and osimertinib was re-administered at a reduced dose of 40 mg every alternate day. The patient had no symptoms, and ECG on days 1 and 5 showed sinus rhythm, no premature ventricular complex (PVC), and no QT prolongation. On day 6, the osimertinib dosage was increased to 40 mg once daily. There were no further events, and ECG on day 19 showed sinus rhythm and no arrhythmia. Following 1 month of treatment with osimertinib, a CT scan revealed a partial response and a decreased CEA level of 11.2 ng/mL. The patient continued to receive osimertinib for 3 months without recurrent syncope.

## Discussion

In this report, we present a case of successful rechallenge with osimertinib after induced ventricular arrhythmia with syncope. While there have been several reports about rechallenge of osimertinib after osimertinib-induced pneumonitis [10, 11], to the best of our

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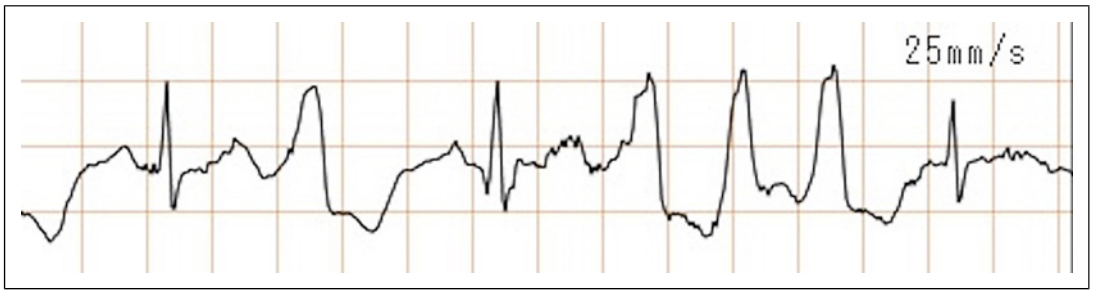


**Fig. 2.** Holter ECG showing non-sustained VT and PVC.

knowledge, this is one of only a few reports on successful rechallenge of osimertinib after induced ventricular tachycardia (VT).

Osimertinib, a third-generation EGFR-TKI with specificity for EGFR T790M mutation, is the first-line treatment of choice for NSCLC with EGFR mutations and T790M mutation-positive NSCLC after first- or second-generation TKI treatment [1, 4]. In our case, osimertinib was administered as the first-line EGFR-TKI. However, due to cardiac events, osimertinib was discontinued, and we switched to erlotinib. Subsequently, liquid biopsy showed a T790M mutation; therefore, osimertinib was the only option among the EGFR-TKIs. Osimertinib was expected to be more effective than cytotoxic chemotherapy. Before osimertinib administration, the risk of recurrent arrhythmias or syncope was fully explained to the patient, and consent was obtained.

Although the incidence of osimertinib-induced cardiotoxicities, including congestive heart failure, QT prolongation, and arrhythmias, is low, these events present a major safety concern due to their life-threatening nature. In the clinical trials of osimertinib (AURA, AURA2, AURA3, FLAURA, and ADAURA trials), cardiac adverse events were reported in 9.9% (5.0–17.2%) of the cases, and none of them caused deaths [2–6]. However, in the clinical setting, sudden death due to QT prolongation has been reported [13]. Furthermore, QT prolongation, VT, and Torsades de pointes were also reported in a limited number of cases during osimertinib administration [8, 9, 14, 15]. In this case, we were unable to detect the arrhythmia at syncope. However, NSVTs monitored by a Holter ECG can be a cause of syncope. Symptoms of NSVT vary and may include palpitations, chest pain, syncope, and its presence may increase the risk for more malignant dysrhythmias such as sustained VT or ventricular fibrillation that can cause sudden cardiac death [16]. Particularly, frequent, polymorphic ventricular arrhythmias, such as the present case, have a statistically significant correlation with sudden cardiac death [17]. Furthermore, since the occurrence of frequent PVCs (≥30/h) was a significant predictor of cardiovascular events [18], our patient, with 2,300 PVCs/hour, was at an extremely high risk for sudden cardiac death.

In previous reports, the median duration from osimertinib initiation to arrhythmia onset was approximately 30 days; however, QT prolongation syndrome developed on day 2, and VT developed on day 4 [19]. In our case, NSVT occurred 10 days after the initiation of osimertinib treatment, which is consistent with a previous report. Furthermore, we considered osimertinib-induced NSVT because it occurred after starting osimertinib at 80 mg, which disappeared after withdrawal, and we could not identify any other causes.

The etiology of osimertinib-induced cardiotoxicity remains unknown. It may be similar to trastuzumab, a monoclonal antibody against human EGFR2 (HER2). HER2 is expressed in multiple-organ systems including the cardiomyocyte membrane and plays a critical role in cardiomyocyte survival, growth, and stress response [20]. Osimertinib inhibits both EGFR and HER2, which may lead to cardiotoxicity. In addition, afatinib inhibits HER2 expression [21].

Case Rep Oncol 2023;16:1100–1106
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There has been a report of heart failure caused by afatinib in 1.88% of patients and a case of suspected medication for PVC [22, 23]. Erlotinib, on the other hand, has been reported to cause thrombotic complications and not heart failure or cardiac conduction defects [24]. This is one of the reasons that we used in this case.

The most common mechanism of acquired resistance to EGFR-TKIs is the appearance of a T790M mutation in the EGFR kinase domain. The T790M mutation inhibits drug binding by steric hindrance and increases the affinity of the kinase for ATP [25]. A meta-analysis of EGFR mutation testing using plasma circulating tumor deoxyribonucleic acid in NSCLC patients showed higher specificity compared to results from tissue samples [26]. Liquid biopsy reveals a mutation profile of circulating tumor cells that can change during treatment, potentially clarifying resistance gene mutations [27]. Furthermore, osimertinib may be an effective treatment option for patients with advanced recurrent NSCLC in whom the EGFR T790M mutation is confirmed by liquid biopsy [28]. In our case, T790M mutation was detected by liquid biopsy after progression of erlotinib treatment. Therefore, subsequent treatment was adjusted to osimertinib.

Although there is no clear evidence, previous reports have indicated that re-administration of osimertinib at half the standard dose (40 mg/day) may be a safe and effective strategy for patients who develop pneumonitis [29, 30]. Furthermore, low-dose administrations of EGFR-TKIs are reportedly effective in patients with EGFR-mutated NSCLC [31, 32]. There is only one report of osimertinib re-administration after cardiotoxicity, and in other reports, osimertinib was stopped and not resumed due to fatal arrhythmias [12]. Our patient was restarted on 40 mg every alternate day because of severe side effects of syncope, although there was no evidence of this. Considering the patient's desire for early discharge, the dose was increased to 40 mg daily on day 6 with close monitoring. Arrhythmia did not recur, and tumor shrinkage was observed.

In conclusion, this case suggests that low-dose osimertinib rechallenge after induced ventricular arrhythmia may be a treatment option; however, osimertinib rechallenge must be carefully selected and monitored based on the risk-benefit analysis.

## Acknowledgment

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## Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

## Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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## Author Contributions

Zentaro Saito drafted the manuscript. Zentaro Saito, Takuma Imakita, and Tadashi Mio were involved in the treatment of the patient. Takanori Ito, Takuma Imakita, Issei Oi, Osamu Kanai, Kohei Fujita, Hiromasa Tachibana, and Tadashi Mio contributed to the manuscript review before submission and approved the final version of the manuscript.

## Data Availability Statement

All available data for this research are included in this article. Further inquiries can be directed to the corresponding author.

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