Cardiac adverse events in *EGFR*-mutated non-small cell lung cancer treated with Osimertinib

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Background

- Osimertinib, a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), inhibits both EGFR-TKI sensitizing and resistant T790M mutations detected in non-small cell lung cancer (NSCLC) patients. Several large clinical trials have shown the superior clinical activity and safety of osimertinib to other previous EGFR-TKIs, which have made osimertinib the standard care for advanced EGFR-mutated NSCLC.
- Cardiac adverse events (AEs) induced by osimertinib are infrequent; however, cases of severe associated cardiac dysfunction have been reported and remain poorly understood.

Objective

- To assess osimertinib-associated cardiac AEs in the real-world setting using a retrospective single-center cohort study in Japan.

Methods

- One hundred twenty-three advanced NSCLC patients with confirmed EGFR mutations who received osimertinib monotherapy from 2014 to 2019 at the Osaka International Cancer Institute (Osaka, Japan) were evaluated. Cardiac AEs were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Changes in left ventricular ejection fraction (LVEF) and rates of CTRCD, defined as a ≥10% absolute decline in LVEF from baseline to a value <53%, were further assessed in 36 patients in whom serial measures of LVEF were obtained prior to and during osimertinib treatment.

Results

Figure 1. Diagram of patient analyses

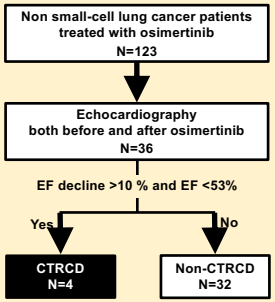
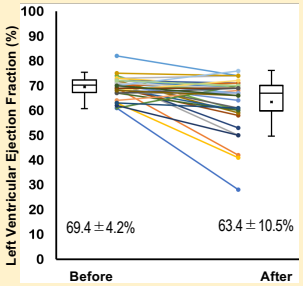


Figure 2. Changes in LVEF before and after osimertinib administration.



- LVEF significantly decreased after osimertinib.

Table 2. Cases of osimertinib induced severe cardiac adverse events

Case	1	2	3	4	5	6
Age, yr	78	71	68	64	52	71
Sex	Female	Female	Male	Female	Female	Female
EGFR mutation	L858R	L858R+T790M	Ex.19 del+T790M	L858R+T790M	L858R	L858R
Osimertinib line / effect	2nd / PR	3rd / PR	3rd / PR	3rd / PR	1st / PR	1st / NE
Tobacco	No	No	No	Yes (former)	Yes (former)	No
CVD risk / history	HTN, Aortic aneurysm operation	HTN	Moderate MR HU	Moderate MR	Obesity	HTN, DM
Daily Medications	Carvedilol 20mg Nifedipine CR 40mg Azilsartan 40mg Rosuvastatin 5mg	Amlodipine 5mg	Allopurinol 100mg Prednisolone 5mg	Prednisolone 7.5mg	-	Candesartan 8mg
Symptoms	External dyspnea Leg edema	Fatigue	Leg edema Fatigue	Facial/leg edema	-	Chest pain Dyspnea
Cardiac event	Heart failure QT prolongation	MR progression Mitral valve prolapse	TR progression	EF decline, HTN MR progression	EF decline	Acute myocardial infraction
CTCAE Grade	3	3	3	3	3	4
Time to event	3 months	3 months	1 month	9 months	2 weeks	2 months
NT-proBNP (pg/ml) or BNP (pg/ml)	NT-proBNP 18890	BNP 21.9	NT-proBNP 450	BNP 227.9	NT-proBNP 36	BNP 423.4
EF prior to Osimertinib (%)	61	82	74	72	63	69
EF after Osimertinib Initiation (%)	28	74	60	50	41	42
CTRCD	Yes	No	No	Yes	Yes	Yes
Valvular disease	MR; none → severe	MR; trace → severe prolapse	TR; trace → moderate to severe	MR; mild to moderate→ moderate	-	-
Osimertinib treatment	Discontinued	Discontinued	Reduced dosage 80 to 40mg every other day	Temporarily held and resumed at 80mg daily	Discontinued	Discontinued
Subsequent cancer therapy	Gefitinib	Gefitinib	Osimertinib rechallenge	Osimertinib rechallenge	Afatinib	Erlotinib
Treatment for Cardiac event	Fulosemide 40mg Spironolactone 50mg Candesartan 5mg Carvedilol 5mg Tolvaptan 7.5mg	Fulosemide 20mg	Fulosemide 40mg Tolvaptan 3.75mg	Fulosemide 20mg Spironolactone 25mg	Candesartan 4mg	PCI for LAD#6
Return of EF to baseline	No; 48% after 9 months	Yes; 74% after 6 months	Yes; 72% after 2 months	Yes; 62% after 14 months	Yes; 63% after 2 months	No; 54% after 7 months

- In the 123 NSCLC patients, severe cardiac AEs (CTCAE grade 3 or higher) occurred in 6 patients (4.9%) after osimertinib administration. Five of the 6 patients had a pre-existing history of cardiovascular risk factors or disease.

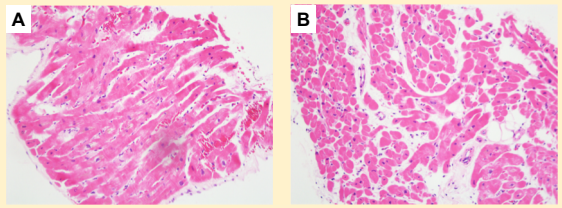
Table 1. Comparison of cardiac function between Non-CTRCD and CTRCD patients

	NSCLC patients (n = 36)			Non CTRCD (n = 32)			CTRCD (n = 4)		
	Before	After	p-value[1]	Before	After	p-value[2]	Before	After	p-value[3]
LVEF (%)	69.4 ± 4.2	63.4 ± 10.5	<0.001	69.8 ± 4.0	67.9 ± 5.5	0.004	66.3 ± 5.1	40.3 ± 9.1	<0.001
LVIDd (mm)	42.6 ± 4.5	44.5 ± 5.2	0.005	42.4 ± 4.4	43.9 ± 4.8	0.003	44.0 ± 4.9	48.8 ± 7.2	0.344
LVIDs (mm)	26.3 ± 3.3	29.1 ± 5.6	<0.001	26.0 ± 3.1	27.8 ± 3.9	<0.001	28.2 ± 4.3	39.3 ± 7.5	0.001
E peak (cm/s)	66.7 ± 18.0	73.4 ± 19.2	0.017	67.3 ± 18.2	73.1 ± 17.9	0.035	62.4 ± 18.1	75.7 ± 31.4	0.858
Dct (ms)	222.6 ± 54.0	217.9 ± 39.2	0.625	225.2 ± 55.9	216.6 ± 31.3	0.333	201.5 ± 32.4	228.5 ± 87.3	0.817
E/A ratio	0.9 ± 0.26	1.04 ± 0.36	0.013	0.9 ± 0.28	1.04 ± 0.38	0.047	0.7 ± 0.14	0.98 ± 0.26	0.870
HR (/min)	74.2 ± 10.8	75.1 ± 14.6	0.600	74.3 ± 11.3	74.3 ± 14.5	0.875	73.4 ± 7.0	81.6 ± 16.5	0.442

[1]p-value comparing cardiac parameters before and after osimertinib in 36 NSCLC patients; [2]p-value comparing cardiac parameters before and after in 32 patients without CTRCD; [3]p-value comparing cardiac parameters after in 32 Non-CTRCD and after in 4 CTRCD.

- In 36 patients with serial LVEF assessment, LVEF declined from 69.4 ± 4.2% to 63.4 ± 10.5% with osimertinib (p<0.001). CTRCD occurred in 4 patients with a nadir LVEF of 40.3 ± 9.1% with osimertinib.

Figure 3. Hematoxylin-Eosin staining of myocardial specimen (200x)



A. Case 1: cardiomyocytes were moderately hypertrophied with disarray and deposition of lipofuscin. There was slight interstitial edema and fibrosis, but no inflammatory cell infiltration.
B. Case 5: cardiomyocytes were mildly hypertrophied with partial vacuolization and deposition of lipofuscin, indicative of myocyte damage. Interstitial edema and fatty infiltration with partial fibrosis were observed around the vasculature, while lymphocyte infiltration was modest

- The common histopathological findings of these patients were cardiomyocyte hypertrophy and lipofuscin deposition.
- Both cases had pre-existing cardiovascular risk factors, including either hypertension or obesity, which may have also worsened or resulted in cardiomyocyte hypertrophy.
- Focal vacuolization and degeneration of myocytes were also observed in Case 5, which is suggestive of myocyte damage, and these change may associate with osimertinib.
- Osimertinib does not result in a pattern of myocyte death seen with anthracyclines nor myocarditis seen with immune checkpoint inhibitors.
- Cardiac dysfunction associated with osimertinib may result from functional inhibition of myocyte contractility without induction of marked cell death or inflammation.

Conclusion

- In our retrospective cohort study, the incidence of cardiac AEs in patients treated with osimertinib was 4.9% that was similar to that observed in the clinical trials.
- Additional prospective data collection of advanced NSCLC patients treated with osimertinib will be important in understanding the incidence, pathophysiology and management of cardiac AEs with osimertinib.

List of abbreviations: **AE**, adverse event; **CTCAE**, common terminology criteria for adverse events; **CTRCD**, cancer therapeutics-related cardiac dysfunction; **EGRF**, epidermal growth factor receptor; **LVIDd** and **LVIDs**, left ventricular internal end diastolic and end systolic diameter; **LVEF**, left ventricular ejection fraction; **MR**, mitral regurgitation; **NT-proBNP**, N-terminal prohormone of brain natriuretic peptide; **NSCLC**, non-small cell lung cancer; **TKI**, tyrosine kinase inhibitor; **TR**, tricuspid regurgitation.

COI Disclosure : The authors have no financial conflicts of interest to disclose concerning the presentation.