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REVIEW

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A systematic review of epidermal growth factor receptor tyrosine kinase inhibitor-induced heart failure and its management

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Abstract

Background: Multiple case reports and case series have been published on heart failure due to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), yet the management and outcome of the said disease have been scarcely discussed in sufficient details. This review is aimed at characterizing the signs, symptoms, laboratory parameters, and outcomes of this entity by analyzing recent published case reports and case series reporting new-onset heart failure in non-small cell lung cancer tumor (NSCLC) patients who are being treated with EGFR TKIs.

Methods: This is a systematic review of case reports and case series for cases of EGFR TKI-induced heart failure. A systematic search was conducted across a number of databases starting with PubMed databases utilizing its MeSH database; after that, a complementary search through Google Scholar was conducted.

Results: In total, 23 cases of epidermal growth factor receptor tyrosine kinase inhibitor-induced heart failure were included. The majority of the reported case were females (20 females and three males) with a male-to-female ratio of 1:6.6. Ages ranged from 47 to 91 years of age with a mean age of 70.73 and a median of 71 years of age. Symptom improvement and being symptom-free from a heart failure perspective after treatment from the acute event were observed in 18 cases (78.26%) while heart failure progressively worsened and led to the death of the patient in only one case (4.3%).

Conclusion: The utilization of EGFR TKIs in NSCLCs has been associated with a better outcome and fewer side effects when compared to classical chemotherapeutic agents. However, cardiotoxic effects, such as heart failure, could be significant for a small proportion of patients. Recent papers have reported heart failure in younger and cardiac risk-free patients. Still, it is only advised to monitor for heart failure in the high-risk group. Treatment should be individualized and based on a case-by-case basis.

Keyword: EGFR, TKI, Cardiotoxicity, Heart failure, Epidermal growth factor, Tyrosine kinase inhibitors

Background

The epidermal growth factor receptor (EGFR) which is a member of the tyrosine kinase receptor family is found to be mutated in approximately 12.5% and 50% of non-small cell lung cancer tumors (NSCLCs) of the Caucasian and Asian populations respectively; thus, it is the most established target for NSCLC therapy [1]. Henceforth, multiple drugs have been produced which target the EGFR such as erlotinib, afatinib, gefitinib, and osimertinib. These targeted therapy drugs have drastically changed the treatment of NSCLC and have become the gold standard of care for patients with NSCLC that have the EGFR mutation [2]. Although they are mostly well tolerated when compared to older chemotherapy agents, they

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might still cause severe side effects in some patients such as cardiotoxicity, hepatotoxicity, and interstitial lung disease [3].

The fact that metastatic cancer patients in general are now surviving for longer has led to the increased recognition of the importance of the cardiotoxicity that is caused by anticancer treatment; with that being said, it is still somewhat disregarded in lung cancer patients due to the dismal survival rate that they used to possess and that highly cardiotoxic anticancer medications such as anthracyclines are not used as much anymore [4]. Anticancer treatment cardiotoxicity is typically classified into two categories; type I cardiotoxicity which is caused by anthracyclines is irreversible and is additive in a dose-dependent manner. On the other hand, type II cardiotoxicity is reversible and is caused by suppression of the HER2 signaling pathway [5].

Multiple case reports and case series have been published on the matter of heart failure due to EGFR TKIs, yet the management and outcome of the said disease have been scarcely discussed in sufficient details. Thus, to help in diagnosing this entity and characterize its signs, symptoms, laboratory parameters, and outcomes leading to successful management for patients, we have conducted this literature review on case reports and case series of "Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors-induced heart failure and its management". We have reviewed patient demographics, imaging findings, tumor characteristics, acute event management, and outcomes of case reports and series that we have found up to the date of this manuscript writing.

Methods

This is a systematic review of case reports and case series for cases of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)-induced heart failure. A systematic search was conducted across a number of databases starting with PubMed databases utilizing its MeSH database; after that, a complementary search through Google Scholar was conducted. This search was conducted in the period between 22/9/2022 and 3/10/2022 using the keywords: "cardiotoxicity," "Heart failure," "EGFR," "cardiac dysfunction," "Osimertinib," "Gefitinib," "Afatinib," "Erlotinib." Following the PRISMA guidelines [6], we presented the flowchart in Fig. 1 demonstrating our search process. In total, we have included 23 cases extracted from 12 case reports, two case series, and two letters to the editor. We have used Microsoft Excel for analyzing the data and measuring the mean, median, and mode of data extracted from the included cases.

We have included case reports, case series, and letters to the editor written in English in which the diagnosis of heart failure post-treatment initiation of EGFR TKI medications has been made on the basis of compatible signs and symptoms of heart failure, a reduction in the ejection fraction of more than or equal to 10% of the baseline, or the development of an ejection fraction less than 45% in patients with no baseline echocardiogram using either transthoracic or transesophageal study for ejection fraction calculation with or without an elevated level of brain natriuretic peptide and with no other discernible causes for the reduction in the ejection fraction. We have excluded studies in which the diagnosis was anything

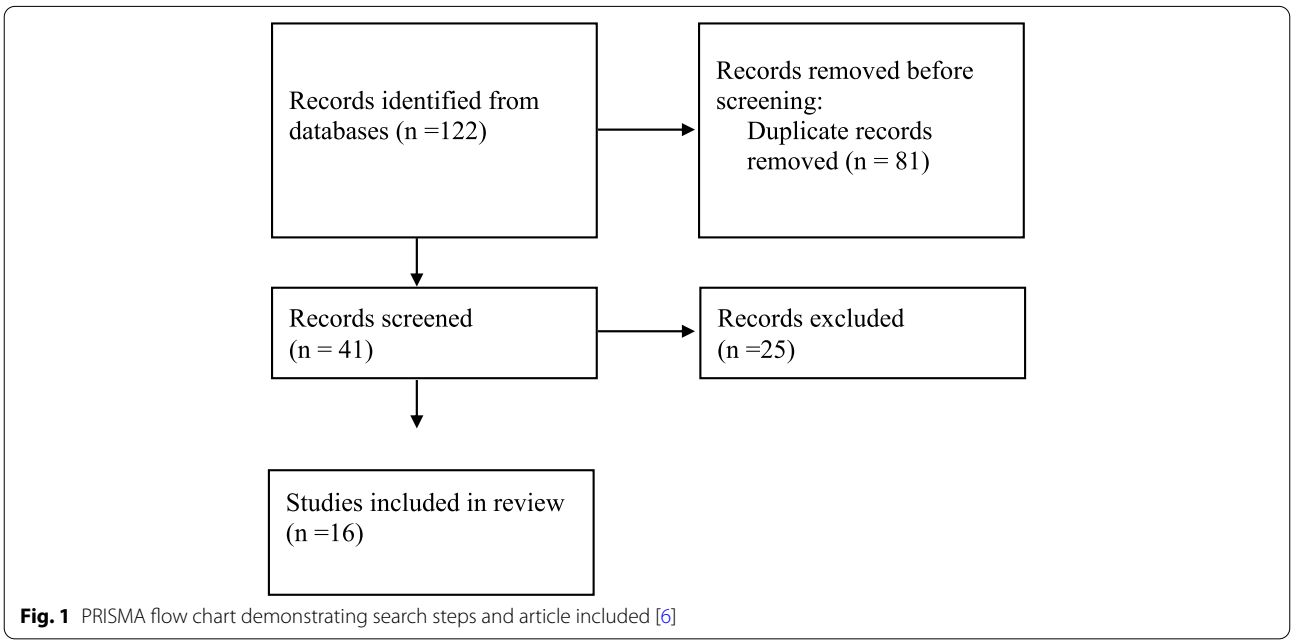

Fig. 1 PRISMA flow chart demonstrating search steps and article included [6]

other than heart failure and studies in which causes other than the anticancer treatment as a trigger of heart failure could be detected.

Results

In total, 23 cases of epidermal growth factor receptor tyrosine kinase inhibitor-induced heart failure were included. Of which, 12 cases were in separate case reports, two were in letters to the editor, and nine were included from two separate case series. The majority of reported cases were females (20 females and three males) with a male-to-female ratio of 1:6.6. The ages ranged from 47 to 91 years of age with a mean age of 70.73 and a median of 71 years of age. Most of the cases reported to suffer from treatment-induced heart failure were treated using osimertinib ($N=19$, 82.6%), two (8.9%) were treated with erlotinib, one case (4.3%) was treated with afatinib, and one case (4.3%) with gefitinib. After the initiation of the treatment, the signs and symptoms of heart failure were appreciated after a period of time that ranged from 2 to 108 weeks with a mean of 25.82 and a median of 20 weeks (Table 1).

The most common identified mutation for NSCLC patients in our study is the T790 mutation affecting 11 patients (47.82%) of our study's population. Other mutations in our study included Exon 21 mutation in seven patients (30.4%) and Exon 19 deletion mutation occurring in six patients (26%),

Most patients (65.2%) had no prior primary cardiac disease while only 34.8% suffered from cardiac disease. The average ejection fraction for patients prior to treatment initiation was 63.9%, the average for the lowest ejection fraction during the treatment was 39.65% with an average drop of the ejection fraction of 21.1 from the baseline, and the average ejection fraction post-treatment termination was 56.05% with an average rise of 15.6. Five patients had a valvular disease prior to therapy initiation and of those patients; four (75%) were reported to have their valvular disease worsen during the treatment period. Two patients developed new-onset valvular disease during treatment.

Only five patients (21.7%) were reported to have a histopathological exam for obtained cardiac tissue sample. Three of the five samples showed no infiltration of the cardiac biopsy with neither inflammatory cells, amyloid deposits, nor necrosis while only one case was reported to have mild fibrosis on histopathological exam and one case was reported to have lymphocytic infiltration of the biopsy.

Treatment of the acute event mostly consisted of regular heart failure exacerbation medications such as angiotensin-converting enzyme inhibitors (ACE-i), loop diuretics, potassium-sparing diuretics, and beta blockers after the patients' condition had stabilized with all cases being treated using the same regime with some modifications to the drugs within the same class and doses of given drugs. The EGFR TKI drug was discontinued in 20 patients, the dose was reduced in two patients, and the drug was replaced with another drug of the same class but a different generation in five cases.

Symptom improvement and being symptom-free from a heart failure perspective after treatment from the acute event were observed in 18 cases (78.26%). Two patients (8.69%) refused additional therapy and were sent into hospice for supportive care and symptoms of heart failure progressively worsened and led to the death of the patient in one case (4.3%).

Discussion

This systematic review is the first in literature to investigate EGFR tyrosine kinase inhibitor-induced heart failure and we included 1st-generation (gefitinib, erlotinib), 2nd-generation (afatinib, dacomitinib), and 3rd-generation (osimertinib) TKIs. Since osimertinib is the most used drug, most of the published literature have investigated this drug's induced heart failure. A literature review by Okuzumi et al. showed similar results to our group regarding the median age and male-to-female ratio. [2] However, all the patients investigated in the review had previous cardiovascular comorbidities which may be predisposed to the development of cardiomyopathy. Our review showed 11 patients of the 19 who were on osimertinib were devoid of any cardiovascular comorbidity. In addition, the median time to event was lower in the review (8 weeks) than in our group (20 weeks).

Non-small cell lung cancers account for up to 90% of all primary lung malignancies. Lung cancers in general are the leading cause of death among malignancies in both males and females. Most patients present at advanced stages, hence the dismal 5-year survival rate of only around 7–35% despite the improvements in our understanding of the entity and new introduced treatments. [21] Primary NSCLC histological types include squamous cell carcinoma and adenocarcinoma. Smoking is an established strong risk factor for the development of NSCLC, as well as exposure to carcinogenic substances such as asbestos, radon, and polycyclic hydrocarbons. Additionally, some genetic elements play an important role in NSCLC development, including EGFR mutations, which may even explain the occurrence of NSCLC in never-smoker patients as they harbor EGFR mutations more frequently. [5]

Heart failure (HF) is a clinical syndrome that develops when the heart's function is impaired and working less efficiently than normal thus it cannot keep up with the metabolic needs of the body [22]. HF has been

Table 1 Cases

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[7]	67, female	No prior primary cardiac disease	Osimertinib	28	–-	Transthoracic echocardiogram (TTE) demonstrated a left ventricular ejection fraction (LVEF) of 70% with left ventricular end-diastolic dimension normal at 35 mm	TTE: global hypokinesis, abnormal global longitudinal strain (− 12%), septal dyssynchrony, and mild biventricular dilation pharmacological nuclear stress test at that time demonstrated a LVEF of 35% with normal perfusion	70%	24%	34%	Lisinopril and metoprolol succinate were initiated, although metoprolol was subsequently discontinued due to fatigue, and lisinopril was replaced by valsartan/sacubitril, Osimertinib was discontinued and replaced by erlotinib	–-	Stable ejection fraction, asymptomatic from a heart failure perspective

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[8]	74, female	No prior primary cardiac disease	Osimertinib	108 (i.e., 2 years)	EGFR gene-positive and T790 mutation-positive	Transthoracic echocardiography demonstrated left ventricular end-diastolic diameter of 43 mm and left ventricular ejection fraction of 63%	Transthoracic echocardiography presented left ventricular end-diastolic diameter of 62 mm and left ventricular ejection fraction of 31%	63%	31%	62%	Osimertinib was terminated, Intravenous diuretics, 2.5 mg of carvedilol. Administration of carvedilol somewhat induced symptomatic hypotension. Termisartan 20 mg was converted to enalapril 1.25 mg. Carvedilol was converted to bisoprolol 1.25 mg, Ivabradine 5.0 mg was initiated to modulate her heart rate	Percutaneous end-myocardial biopsy revealed slight myocardial fibrosis and atrophy without infiltration of inflammatory cells, The electron microscopy showed hypertrophy and variety in size of the myocardium accompanying smaller mitochondria	Asymptomatic from a heart failure perspective
[9]	76, female	No prior primary cardiac disease	Osimertinib	16	T790M *EGFR* mutation	–-	Echocardiogram indicated an obvious finding of severe hypokinesis, with an ejection fraction of 17% and left ventricular enlargement	–-	17%	–-	Osimertinib was discontinued. The patient was treated with furosemide, carvedilol, and enalapril	endomyocardial biopsy confirmed non-specific cardiomyopathy, without inflammatory cell infiltration, amyloid deposits, and necrosis	Return of echo parameters back to normal, with the patient being asymptomatic from a heart failure perspective

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[10]	80, female	No prior primary cardiac disease	Osimertinib	8	EGFR exon 19 deletion	Transthoracic ultrasound cardiography (UCG) showed a left ventricular end-diastolic diameter of 47 mm and an LVEF of 65%	Transthoracic UCG showed a dilated and diffusely hypo-contractile left ventricle (left ventricular end-diastolic diameter 56 mm, LVEF 35%)	65%	35%	62%	Osimertinib discontinued, furosemide intravenously on admission and changed to oral azosemide and spironolactone on the sixth hospital day, oral enalapril maleate and bisoprolol fumarate on the fourth hospital day	—	Asymptomatic from a heart failure perspective, She did not receive any other chemotherapy and died of cancer progression and cachexia at home 15 months after osimertinib discontinuation
[5]	91, male	No prior primary cardiac disease	Osimertinib	6	*EGFR* exon *21 L858R* point mutation	TTE showed normal wall motion of the left ventricle with an LVEF of 64% and normal chamber calibers	TTE showed diffuse hypokinesis of the left ventricular wall, with a decreased LVEF to 48%	64%	48%	63%	Osimertinib was withheld, furosemide (40 mg daily) was administered for four days. In addition, the dosage of azosemide and tolvaptan was increased to 60 and 7.5 mg, respectively	—	Asymptomatic from a heart failure perspective

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[11]	70, female	Mild mitral, and mild tricuspid regurgitation	Osimertinib	24	Epidermal growth factor receptor (EGFR) Exon 21 mutation	Transthoracic echocardiogram showed a left ventricular ejection fraction greater than 55%, mild mitral, and mild tricuspid regurgitation	Transthoracic echocardiogram (TTE) showed mild to moderate left ventricular systolic dysfunction with an estimated left ventricular ejection fraction (LVEF) of 40–45%, moderate to severe tricuspid regurgitation, mild to moderate mitral regurgitation, mild aortic regurgitation	55%	43%	—	treated with electrolyte replacement along with parenteral nutrition initially. The potassium level improved to 4.0 mmol/L over the next 24 h. Repeat EKG (Figure-3) with a potassium level of 3.7 mmol/L still showed a prolonged QTc interval of 552 ms. QTc interval normalized in the next 72 h to 408 ms, Osimertinib dose was decreased to 40 mg at the time of discharge,	—	the patient refused further cancer treatment and decided to go on for hospice management with supportive care

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[12] patient 1	78, female	Thoracic aortic aneurysm	Osimertinib	12	*EGFR* L858R, exon 21	Echocardiography shows a baseline LVEF was 61% and LVIDd/LVIDs were 44/29 mm	Echocardiography revealed severely reduced LVEF at 28% and an increased LVIDd/LVIDs at 44/38 mm, with moderate to severe mitral regurgitation (MR)	61%	28%	48%	Osimertinib was discontinued, and furosemide 40 mg, spironolactone 50 mg, tolvaptan 7.5 mg, carvedilol 5 mg, and candesartan 2 mg, daily	–-	Improvement of the patient's heart failure symptoms
[12] patient 2	68, male	Moderate aortic regurgitation	Osimertinib	4	*EGFR* Ex.19 del. and T790M mutations	Echocardiogram showed a LVEF of 74%	Echocardiography revealed severe tricuspid valve regurgitation (TR) and mild pulmonary hypertension (estimated pulmonary artery systolic pressure: 45 mm Hg)	74%	60%	72%	Osimertinib was discontinued, and tolvaptan 3.75 mg, and furosemide 40 mg daily	–-	fatigue and edema improved, but severe TR persisted
[12] patient 3	64, female	Moderate mitral regurgitation	Osimertinib	36	*EGFR* L858R and T790M mutations	Echocardiography showed moderate mitral regurgitation	Echocardiography showed a LVEF of 50%	72%	50%	62%	Osimertinib was discontinued, and she was treated with furosemide 20 mg; and spironolactone 25 mg daily	–-	Follow-up showed there were no signs of additional cardiac dysfunction

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[12] patient 4	52, female	No prior primary cardiac disease	Osimertinib	2	*EGFR* L858R mutation	Echocardiography revealer a LVEF of 41%	Echocardiography revealed a LVEF of 63%	63%	41%	63%	Osimertinib was discontinued and candesartan 4 mg daily, was initiated	–-	The patient was then treated with afatinib, a second-generation of EGFR-TKI, and her cardiac function remained stable
[13]	73, female	No prior primary cardiac disease	Osimertinib	4	T790M mutation	–-	Echocardiogram revealed left ventricular akinesis from the apical to the midventricular portion, The left ventricular dimension increased from 34 mm preosimertinib treatment to 46 mm, and left ventricular ejection fraction (LVEF) was 58%	75%	58%	64%	Discontinuing osimertinib and adding treatment for heart failure including spironolactone 25 mg and bisoprolol 1.25 mg	–-	diagnosed with asymptomatic TC, and osimertinib treatment was subsequently stopped
[14]	62, female	No prior primary cardiac disease	Osimertinib and ibandronate	24	L858R mutation in exon 21 of the EGFR gene	–-	Echocardiogram indicated an obvious severe hypokinesis, with a left ventricular ejection fraction (LVEF) of 36% and the left ventricle was dysfunctioning	–-	36%	66%	Discontinue osimertinib, furosemide (20 mg bid), spironolactone (20 mg bid), bisoprolol (20 mg qd), and valsartan (50 mg bid) were given	–-	follow-up treatment that included alternative third-generation EGFR-TKI aumolertinib significantly soothed the condition of a patient with no further complaints of heart discomfort, except fatigue

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[15]	70, female	No prior primary cardiac disease	Erlotinib	8	EGFR deletion mutation in exon 19	Echocardiogram showed a LVEF of 67%	Echocardiography, the left ventricular ejection fraction (LVEF) 35%	67%	35%	50%	Treated with carperitide, enalapril, spironolactone, carvedilol, and furosemide	endomyocardial biopsy was performed, and showed myocyte disarray with nuclear pleomorphism and mild fibrosis within the myocardium, No inflammatory cell infiltration, amyloid deposits, or necrosis were observed	The patient was able to continue erlotinib treatment for 9 months without acute exacerbation of chronic heart failure, but due to cancer progression, her anticancer drug was switched to osimertinib, and cardiac function was maintained until the end of the follow-up period
[16]	71, female	Asymptomatic left bundle branch block	Erlotinib	104	–-	–-	TTE showed dilated cardiomyopathy with a left ventricular ejection fraction (LVEF) of 45% and septal dyskinesia without pericarditis	–-	25%	45%	Erlotinib was discontinued, angiotensin-converting enzyme inhibitor, furosemide, bisoprolol and low-salt diet was reinforced	–-	Asymptomatic from a heart failure perspective
[17]	71, female	atrial fibrillation	Afatinib	4	EGFR-mutated lung cancer exon 19 deletion	Echocardiography showed a left ventricular ejection fraction (LVEF) of 60%	Echocardiography showed a decreased LVEF 40%, diastolic dysfunction, left ventricle enlargement, and pericardial effusion	60%	40%	60%	Afatinib was discontinued and alternative therapy with gefitinib 250 mg/d was started	–-	there was no symptom of cardiac dysfunction and an echocardiography showed no change

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[18]	56, female	No prior primary cardiac disease	Gefitinib	28	*EGFR* exon 19 deletion	–-	Transthoracic echocardiography showed diffusely depressed left ventricular wall motion (left ventricular ejection fraction: 28%) with minor pericardial effusion. The left ventricular diastolic diameter was 51 mm, with normal wall thickness	–-	28%	58%	Gefitinib was discontinued and an angiotensin-conversion enzyme inhibitor and beta-blocker were initiated	myocardial biopsy displayed no cardiac hypertrophy, cardiac fibrosis, myocyte disarray, or inflammatory cell infiltration	After discontinuation of gefitinib treatment, her symptoms gradually improved
[19]	84, female	No prior primary cardiac disease	Osimertinib	34	*EGFR* exon 19 deletion and a Thr790Met mutation	–-	Transthoracic echocardiography showed a dilated and diffusely hypocontractile left ventricle (ejection fraction 33%) with minor pericardial effusion. The left ventricular diastolic diameter was 54 mm, with normal wall thickness	–-	33%	33%	Osimertinib was discontinued and furosemide, enalapril, and carvedilol were initiated	Pathological examination of a myocardial biopsy specimen revealed no cardiac muscle hypertrophy, cardiac fibrosis, or myocyte disarray; however, there was lymphocyte infiltration and edematization	After 12 weeks, the left ventricular ejection fraction and cardiothoracic ratio had not changed; however, the patient's facial edema had improved

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[20] patient 1	70, male	No prior primary cardiac disease	Osimertinib	12	EGFR-mutation, T790M mutation on exon 20	Echocardiographic exam showed 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%)	echocardiographic re-evaluation was performed and revealed an ejection fraction of 45%	60%	45%	48%	Medical treatment for cardiac failure was prescribed with furosemide, low-dose angiotensin-converting enzyme inhibitor (ACEi), ramipril 2,5 mg, bisoprolol 1,25 mg daily and osimertinib was discontinued	–-	Symptoms and clinical conditions progressively worsened, despite medical treatment and osimertinib withdrawal. And patient past away 4 weeks after drug discontinuation

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[20] patient 2	73, Female	intermittent left bundle branch block, mild mitral valve insufficiency due to leaflets fibrosis	Osimertinib	8	T790M	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 mitral valve insufficiency due to leaflets fibrosis was present	Echocardiography showed a global left ventricular dysfunction with an ejection fraction of 50%, mitral valve insufficiency worsened becoming moderate together with an increase in filling pressure	62%	50%	62%	Osimertinib was suspended for 3 weeks and betablocker (bisoprolol1,25 mg per day) was administered	–-	,osimertinib was restarted at the same dosage without any heart failure symptoms
[20] patient 3	47, Female	No prior primary cardiac disease	Osimertinib	20	T790M	Baseline echocardiographic evaluation did not show any pathological finding. With an ejection fraction of	Echocardiogram showed an ejection fraction of 51%	64%	51%	60%	Bisoprolol (5 mg/day) and perindopril (5 mg/day) were administered	–-	4 weeks after the event osimertinib restarted, the patient underwent a full recovery of the systolic function

Table 1 (continued)

Reference	Age and sex	Prior primary cardiac disease	Drug used	Duration of treatment before heart failure detection in weeks	mutation	Imaging modalities and findings before medication	Imaging modalities and findings while on medication	Ejection fraction before starting drug (baseline)	Lowest ejection fraction while using the drug	Ejection fraction after discontinuing the drug	Treatment for event	Histopathology report	Outcome
[20] patient 4	71, Female	No prior primary cardiac disease	Osimertinib	36	T790M	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	Echocardiogram showed an ejection fraction of 45%. Left ventricle and left atrium volumes were both mild dilated (LAVol/BSA: 42 ml/m2; LVVol D/BSA: 83 ml/m2)	58%	45%	54%	Bisoprolol 2,5 mg/daily, furosemide 12,5 mg/daily, and perindopril 2,5 mg/daily	––	Fifteen days after interruption,osimertinib therapy was resumed along with cardiologic therapy prosecution. Clinical and echocardiographic controls showed a stabilization of the cardiac function
[20] patient 5	80, Female	No prior primary cardiac disease	Osimertinib	44	T790M	Echocardiographic evaluation did not show any pathological findings. And an ejection fraction of 62%	Echocardiogram showed an ejection fraction of 43% and an increase in left ventricle mass and left atrial volume	62%	43%	55%	. Osimertinib was temporarily suspended and enalapril therapy titrated from 2,5 mg to 5 mg per day	––	Reduced osimertinib dose at 40 mg/die with a stable echocardiographic monitoring until the treatment was permanently discontinued for progressive disease

considered a major public health issue in recent years due to its growing prevalence [23]. With significant rates of morbidity and mortality, patients have a wide array of clinical presentations of HF. However, patients mainly present with symptoms of dyspnea, exercise intolerance, and edema [24]. HF most commonly develops as a result of cardiovascular diseases such as myocardial ischemia or infarction, hypertension, cardiomyopathies, and valvular heart diseases [25]. However, there are less common etiologies like drug-induced heart failure [26], which may arise due to the direct cardiotoxic effects of some drugs or drug-drug interactions. Many studies have shown that tyrosine kinase inhibitors (TKI) are associated with cardiotoxic effects [27]. The current systemic review highlights the reported cases of epidermal growth factor receptor tyrosine kinase inhibitor-induced heart failure and its management.

Epidermal growth factor receptor (EGFR) has been identified as a member of the ErbB family of receptors, which is made up of four distinct types of receptor tyrosine kinases (RTK): the previously mentioned EGFR as ErbB-1, ErbB-2, ErbB-3, and ErbB-4 [28]; it has been recognized that protein kinases contribute to several cellular functions that include proliferation and differentiation through multiple mechanisms [29]. RTK works by the activation of many pathways through a ligand that binds to an extracellular domain of a receptor that is located on the membrane, which activates the intrinsic kinase tyrosine residues and induces activation of downstream signaling pathways [30]. With that being said, EGFR plays a crucial role in the pathogenesis of several malignancies [28].

EGFR tyrosine kinase inhibitors (EGFR TKI) are Food and Drug Administration (FDA) approved for the treatment of many cancers including non-small cell lung cancer (NSCLC); these drugs bind to tyrosine kinase domain by competing with ATP. Thus, inhibiting autophosphorylation [31], this results in the reduction of the proliferation, invasion, and angiogenesis of the tumor [32]. Gefitinib and erlotinib both inhibit the kinase activity reversibly and are considered a first-generation class, while second- and third-generation afatinib, dacomitinib, and osimertinib are irreversible EGFR TKI [31]. Commonly reported side effects of EGFR TKI drugs include diarrhea, rash, acne, and stomatitis [33]. Dose management and supportive care showed a significant reduction in both the intensity and frequency of said side effects [34].

Although EGFR TKI medications have provided massive strides in cancer treatment and are considered to be much safer than classic chemotherapy agents, they have been reported to cause life-threatening side effects including cardiotoxicities [35]. The effect of EGFR TKI medications on the heart ranges from an asymptomatic prolongation of the QT interval to symptomatic heart failure and even cardiovascular collapse [27].

Uncertainty surrounds the detailed mechanism. A signal cascade that has a strong association with the homeostasis of the myocardium might be suppressed by EGFR TKIs. Furthermore, EGFR TKI might inhibit the proper activity of mitochondria and cause their apoptosis and suppress the HER2 receptor, which may also prevent the proper myocardial differentiation [8].

The current systematic review revealed that patients treated with osimertinib were more likely to experience heart failure compared to patients that received erlotinib, afatinib, and gefitinib. There was a comparison between osimertinib cardiotoxicity and other EGFR TKIs (erlotinib, afatinib, gefitinib) that provides supports to these article findings [36]. Data collected retrospectively from 2016 to 2018 indicated a significant increase in the risk of QT prolongation, heart failure, and atrial fibrillation associated with osimertinib when compared to other EGFR TKIs. Out of 8450 reported adverse events related to EGFR TKIs, 2454 were due to the treatment with osimertinib, whereas 5836 were associated with other EGFR TKIs (erlotinib, afatinib, gefitinib) [37]. According to a retrospective review of the FDA side effects reporting system, an incidence of 2.3% of heart failure during the treatment with osimertinib has been reported [36]. In another Japanese report, 2.5% of the patients suffered from heart failure during osimertinib course [38]. A meta-analysis showed that osimertinib had a significant association with QT prolongation and increased hazard for heart failure as well [39].

A female majority treated with osimertinib that suffered from drug-induced heart failure symptoms was observed in the cases included in the analysis. From the total number of adverse events related to osimertinib, 80.3% of patients experienced heart failure and 67.9% of patients suffered from QT prolongation were females [36]. The type of the mutation in the EGFR could be responsible for the apparent difference in the cardiotoxicity side effect. In a study including 33 persons with Del-19 mutation, 23 patients have shown partial response to EGFR TKI comparing to only 7 patients out of 18 patients with other mutations [40]. Moreover, sensitivity to EGFR TKI and increase in survival time were associated with female sex, which could further justify the higher prevalence of cardiotoxicity among the female gender [41, 42].

For early diagnosis and prompt therapeutic intervention, it is advised to screen potential high-risk patients and carefully monitor them using newly proposed echocardiography strain patterns and troponin levels [43]. In the present review, the general management of TKI-induced cardiac toxic effects after the initiation of the

treatment depended mainly on overcoming the symptoms of heart failure and improving patients' treatment outcomes. For that angiotensin-converting enzyme inhibitors (ACE-i), loop diuretics, potassium sparring diuretics, and beta blockers were prescribed based on the stability of patients' condition. Osimertinib was terminated in 87% of the cases, dose decreased from 80 to 40 mg in two cases, and other EGFR TKIs were either terminated or changed to another drug from the same category in five cases. After treatment modification, the majority of cases experienced an average rise of 15.6% in LVEF. At the end of the treatment, 78.26% of the patients' heart failure symptoms were improved or became symptoms free, 8.69% of the patients' symptoms worsened, and one patient passed away.

Given its dose-independency, the discontinuation of osimertinib might aid in the restoration of cardiac function. Kunimasa and colleagues reported three patients whose LVEF recovered at least partially by 1–3 months following the termination of osimertinib [38]. Henceforth, patients receiving osimertinib are recommended to undergo regular echocardiogram monitoring for LVEF at baseline and every 3 months. When the LVEF falls below 50% and by 10% from baseline values, withholding osimertinib is highly considered [44].

Conclusion

In conclusion, the utilization of EGFR TKIs in NSCLCs has been associated with a better outcome and fewer side effects when compared to classical chemotherapeutic agents. Still, however, cardiotoxic effects, such as heart failure, could be significant for a small proportion of patients. It was suggested that EGFR TKI-induced heart failure involves patients with established cardiovascular risks. Nevertheless, recent papers have reported heart failure in patients who do not have these risks. Since these cases are the exception, it is only advised to monitor for heart failure in the high-risk group. Treatment should be individualized, which could involve only symptomatic treatment with medications, changing the TKI to another drug of the same category, reducing the dose, or terminating the offending drug.

Limitations

Due to the fact that this is a systematic review based on case reports, case series, and letters to editors, it is vulnerable to selection bias and is unable to establish a causal relationship between EGFR TKI medications and heart failure since the cases are rare. Many reported cases lacked certain information regarding the clinical features of the case, histopathology results, and procedures performed such as a diagnostic left heart cath.

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Authors' contributions
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