ARTÍCULO DE REVISIÓN

Chemotherapy-Induced Cardiotoxicity in Lung Cancer Patients: A Systematic Review of Case Reports

Cardiotoxicidad inducida por la quimioterapia en pacientes con cáncer de pulmón: una revisión sistemática de informes de casos

Muzakkir Amir[1], Irawaty Djaharuddin[2], Siti Ayu Saputri[2], Andriany Qanitha[1,3,4]

SUMMARY

Cardiotoxicity is one of the most relevant complications associated with the use of chemotherapeutic agents due to their adverse effects on a patient's prognosis and quality of life. This review aimed to capture the clinical profile of patients with advanced lung cancer with chemotherapy, as well as to summarize the type, risk factors, incidence, management, and outcomes of chemotherapy-related cardiotoxicity. From systematic searching, we included ten articles. The mean age of all case reports was 60.1 ± 6.9 years, and 90 % of cases were male. The majority (60 %) of lung cancer reported in this review was non-small cell carcinoma (NSCC). The most widely used chemotherapy was platinum-based regimens. Types of cardiotoxicities found were myocardial infarction (50 %), arrhythmia (20 %), cardiomyopathy (10 %), acute pericarditis (10 %), and Kounis Syndrome (10 %)—around 40 % of cases discontinued chemotherapy agents due to cardiovascular side effects. Patient-related factors, including age, previous cardiovascular disease, adjuvant radiation therapy, metabolic abnormalities, and hypersensitivity to the regimens, were determinants related to cardiotoxicity. Understanding the risk factors, management, and outcomes for cardiotoxicity-related chemotherapy could be influential in preventing and reducing the side effects of this complication, as well as improving patients' quality of life.

Keywords: *Lung cancer, chemotherapy, cardiotoxicity.*

RESUMEN

La cardiotoxicidad es una de las complicaciones más relevantes asociadas al uso de agentes

ORCID: 0000-0002-4914-3542[1]
ORCID: 0000-0002-5240-4950[2]
ORCID: 0000-0003-2420-0560[4]

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar 90245, Indonesia
[2]Department of Pulmonology and Respirology Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar 90245, Indonesia

[3]Department of Physiology, Faculty of Medicine, Universitas Hasanuddin, Makassar 90245, Indonesia
[4]Doctoral Study Program, Faculty of Medicine, Universitas Hasanuddin, Makassar 90245, Indonesia

Corresponding author: *Andriany Qanitha, MD, MSc, PhD
Faculty of Medicine, University of Hasanuddin
Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, South Sulawesi, Indonesia. E-mail: a.qanitha@unhas.ac.id
Tel.: +628114442501
Contributing Authors:
[1]MD, PhD, FIHA
[2]MD, PhD, FAPSR. E-mail: irawatydjaharuddin@unhas.ac.id
[3]MD. E-mail: ayusaputri87@gmail.com

quimioterapéuticos debido a sus efectos negativos sobre el pronóstico y la calidad de vida de los pacientes. Esta revisión tuvo como objetivo capturar el perfil clínico de los pacientes con cáncer de pulmón avanzado con quimioterapia, así como resumir el tipo, los factores de riesgo, la incidencia, el tratamiento y los resultados de la cardiotoxicidad relacionada con la quimioterapia. A partir de la búsqueda sistemática, se incluyeron 10 artículos. La edad media de todos los informes de casos fue de 60,1 ± 6,9 años y el 90 % de los casos eran hombres. La mayoría (60 %) del cáncer de pulmón informado en esta revisión fue carcinoma de células no pequeñas (NSCC). La quimioterapia más utilizada fueron los regímenes basados en platino. Los tipos de cardiotoxicidad encontrados fueron infarto de miocardio (50 %), arritmia (20 %), miocardiopatía (10 %), pericarditis aguda (10 %) y síndrome de Kounis (10 %). Alrededor del 40 % de los casos interrumpieron los agentes de quimioterapia debido a los efectos secundarios cardiovasculares. Los factores relacionados con el paciente, como la edad, la enfermedad cardiovascular previa, la radioterapia adyuvante, las anomalías metabólicas y la hipersensibilidad a los regímenes fueron determinantes relacionados con la cardiotoxicidad. La comprensión de los factores de riesgo, el tratamiento y los resultados de la quimioterapia relacionada con la cardiotoxicidad podría influir en la prevención y reducción de los efectos secundarios de esta complicación, así como en la mejora de la calidad de vida de los pacientes.

Palabras clave: *Cáncer de pulmón, quimioterapia, cardiotoxicidad.*

INTRODUCTION

Lung cancer is one of the most prevalent cancers in the world (1). At the time of initial diagnosis, especially in low- and middle-income countries, most patients are already at an advanced stage, and systemic palliative treatment is the only option left. Current systemic therapy for lung cancer is chemotherapy with various types of regimens, targeted therapy, and immunotherapy (1,2).

Chemotherapy significantly improves the patients' outcomes and is a fundamental element in treating several types of cancer (3). However, the chemotherapy agents do not only work on cancer cells but also on normal cells, especially on fast-growing cells, causing toxicity or side effects that require special attention (2). Many side effects are associated

with chemotherapy, significantly diminishing these agents' use (3). Cardiotoxicity is one of the most relevant complications associated with the use of certain chemotherapeutic agents due to their adverse effects on prognosis and quality of life. Cardiomyopathy, congestive heart failure, pericarditis, myocarditis, and acute coronary syndrome are complicated cardiotoxicity due to chemotherapy (4). Several studies have demonstrated cardiotoxicity associated with some chemotherapeutic agents. This review aimed to summarize the recent literature reporting cardiotoxicity in lung cancer patients who received chemotherapy.

MATERIALS AND METHODS

Searching Strategy

A systematic search of case reports was conducted in January 2022 in the PubMed, Science Direct, and Google Scholar electronic databases published in 2012-2021. In 2024, an additional search was made and two important revisions related to the subject were included in the discussion. We used a set of keywords, including lung cancer, lung carcinoma, chemotherapy, cardiotoxicity, and case report. An independent search was performed, and then we identified and removed some duplicates, screened the studies by title/abstract, and reviewed the complete text, considering inclusion and exclusion criteria based on eligibility. Eligible articles were carefully reviewed to get the essence of data, discussion, and some important points from each reference according to the research objectives.

Detailed information regarding the search strategy is presented in Table 1. Articles were searched independently by two investigators (AQ and SAS), and all included abstracts were exclusively collected using the Rayyan – Intelligent Systematic Review application (https://www.rayyan.ai) for further screening.

Eligibility Criteria

Studies are eligible for inclusion if they meet the following criteria: 1) the articles should be a case report; 2) written in English; 3) publish between 2012 and 2022; 4) reported lung cancer

patients who undergoing systemic chemotherapy; and 5) reported documented cardiovascular side effects. We excluded the articles if the full text was unavailable or if the descriptions of cardiotoxicity or chemotherapy regimens were unclear.

Study Selection

Following the initial literature search, AQ and SAS independently screened the titles and abstracts. Any disagreements that emerged during this screening process were resolved through mutual consensus. We utilized Mendeley Desktop Ver. 1.19.8 for Mac to eliminate duplicate articles and to conduct a comprehensive review of the full manuscripts. Studies that met the predetermined eligibility criteria were included, while those failing to meet the criteria were excluded, accompanied by explicit explanations for their exclusion. Any conflicts in the selection of studies were thoroughly discussed until a consensus was reached.

Data Extraction

Three investigators (MA, SAS, and AQ) individually reviewed the full-text articles and conducted data extraction for each individual study. Any inconsistencies or discrepancies in the data were resolved by referring to the original articles. A standardized data extraction method was employed, utilizing Microsoft Excel.

RESULTS

In the initial literature search, we obtained 314 articles. After removing 19 duplications, 243 articles were obtained for the screening process. A total of 233 articles were excluded after the eligibility process according to the inclusion and exclusion criteria, and finally, we included 10 case reports.

The mean sample age of all case studies in this review was 60.1 ± 6.9 years, with 90 % male cases. The majority (60 %) of cases showed a non-small cell carcinoma, including adenocarcinoma and squamous cell carcinoma, and the remaining 30 % showed a small cell carcinoma type. However,

1 case (10 %) did not clearly state the type of lung cancer.

The combination of chemotherapy agents received in each case report is detailed and described in Table 2. Four cases (40 %) received Cisplatin + Etoposide, and two (20 %) received Cisplatin + Pemetrexed. Cardiovascular toxicities that occurred following an administration of chemotherapy regimens in each case are also shown in Table 2. Five cases (50 %) experienced an acute myocardial infarction, two cases (20 %) had arrhythmia, and the other instances experienced cardiomyopathy, acute pericarditis, and kounis syndrome. Kounis syndrome is the concurrence of acute coronary syndrome with conditions associated with mast cell activation, such as allergies or hypersensitivity and anaphylactic or anaphylactoid.

A simultaneous combination of chemotherapy and radiotherapy (concurrent chemo-radiotherapy) was found in one out of 10 cases; the chemotherapy regimen given was a combination of Cisplatin and Etoposide. Meanwhile, a history of radiotherapy before chemotherapy was reported in two cases, given four years and four months before chemotherapy, respectively.

The cardiovascular risk factors of all patients are reported in Table 3. Majority of cardiovascular risk factors and events in lung cancer patients with chemotherapy were smoking (33.3 %), hypertension (22.2 %), peripheral arterial disease (5.5 %), arrhythmia (5.5 %), post-myocardial infarction (5.5 %), type 2 diabetes mellitus (5.5 %), chronic kidney disease (5.5 %), hypercholesterolemia (5.5 %), and history of venous thrombosis (5.5 %). A combination of more than one cardiovascular risk factor was found in 5 cases (50 %). Five cases reported the initial examination as baseline cardiovascular disease before the administration of chemotherapy. Of all, 4 cases showed normal initial examinations.

Follow-up of cardiotoxicity events due to chemotherapy reported in all case reports varied; amongst others, 4 cases (40 %) completely stopped the chemotherapy regimens with improved patient outcomes. One case remained to continue the radiotherapy with cardiac adjustment doses; 2 cases continued the chemotherapy (1 case improved with bisoprolol

Table 1. Searching Strategy Used in Database

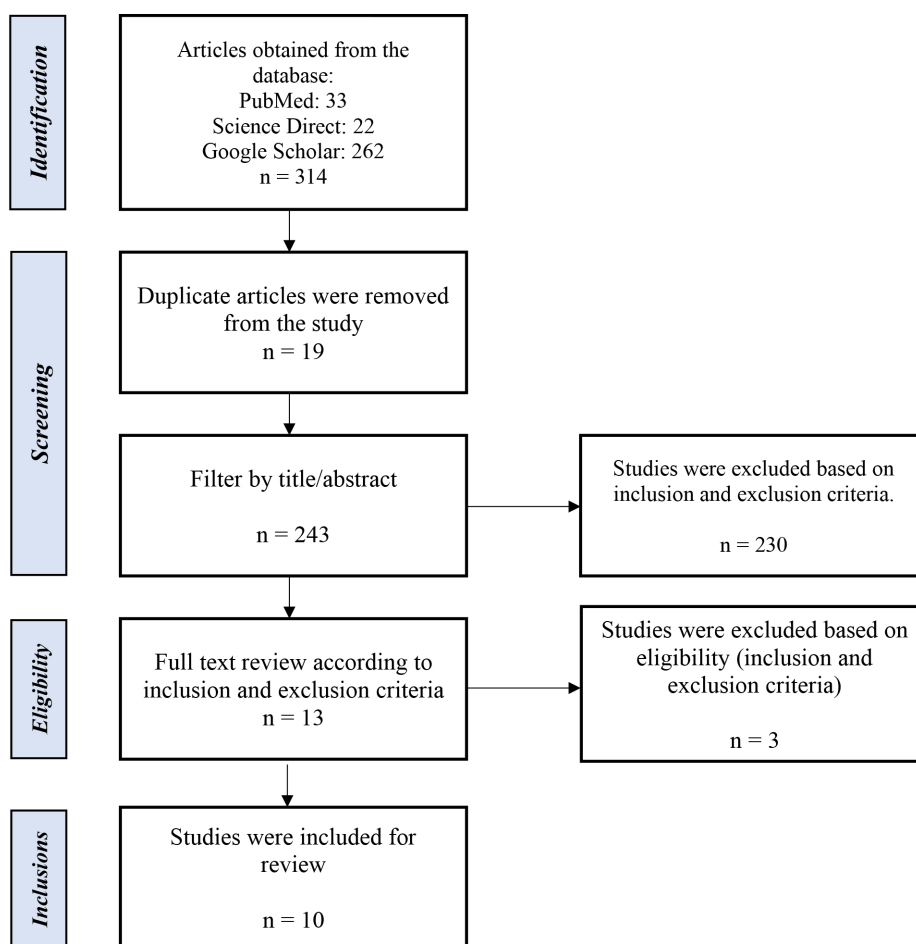|	
PubMed	"lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields] OR ("lung"[MeSH Terms] OR "lung"[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR " carcinomas"[All Fields] OR "carcinoma s"[All Fields]) AND "chemotherapy s"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapies"[All Fields] OR "drug therapy"[MeSH Subheading] OR "chemotherapy"[All Fields] AND "cardiotoxic"[All Fields] OR "cardiotoxicity"[MeSH Terms] OR "cardiotoxicity"[All Fields] OR "cardiotoxicities"[All Fields] OR "cardiotoxity"[All Fields] AND "case reports"[Publication Type] OR "case report"[All Fields] Filter: Publication date 2012 - 2021
Science Direct	"Lung Cancer" OR "Lung Carcinoma" AND "Chemotherapy" AND "Cardiotoxicity" AND "Case Report" Filters: Publication date 2012 – 2021, Case Report
Google Scholar	"Lung Cancer" OR "Lung Carcinoma" AND "Chemotherapy" AND "Cardiotoxicity" AND "Case Report" Filters: Without "Immune Check Point Inhibitor", Publication date 2012 - 2021

Figure 1. PRISMA flow chart for selected studies.

Table 2. Characteristics of case reports included in this review

Author, Year	Age (years), Gender	Types of Lung Cancer	Cardiovascular Side Effects	Chemotherapy Regimen (Dose)	Onset	Radiotherapy	Cardiovascular Risk Factors	Initial Cardiovascular Examination (Baseline)	Therapy on Follow-up	Therapy on Follow-up
Zerna et al., 2014 (5)	70, male	Non-Small Cell Carcinoma cT0rcN2rcM1b	Myocardial Infarction	Vinorelbine / History of Carboplatin + Paclitaxel chemotherapy for three months, four years previously	Three days after chemotherapy cycle 1	Prior radiotherapy 60 Gy Four years before	Smoking, hypertension, hypercholesterolemia, peripheral artery disease	None	Aspirin,clopidogrel, simvastatin, bisoprolol, ramipril PCI and right coronary artery thrombolysis	Improved
Oyakawa et al., 2017 (6)	59, female	Stage IV Adenocarcinoma (T4N3M1a)	Cardio-myopathy	Cisplatin (75 mg/m²) and Pemetrexed (500 mg/m²) per 3 weeks for four cycles, followed by Pemetrexed 500 mg/m²) per 3 weeks	During cycle 17, pemetrexed single chemotherapy	None	Venous thrombo-embolism	None	Chemotherapy was discontinued / Furosemide, enalapril, carvedilol	Improved / Echocardiography: decreased left ventricular size (diameter 58mm), LV EF 33%
Huang et al., 2022 (7)	69, male	Adenocarcinoma Stage IIIb (cT2aN3M0)	Arrhythmia (PVC)	Cisplatin (H-1, 45 mg; H2 and 3, 40 mg) and Pemetrexed (H-1 840 mg)	On day 1 of cycle one chemotherapy, getting worse on day 3 of cycle one chemotherapy	None	Smoking, arrhythmia	Yes (PVC)	Permetrexed single chemotherapy / Buccinnazine 100 mg	Improved
Bursac, 2018 (8)	58, male	Squamous cell carcinoma Stage IIIb (T2aN3M0)	Myocardial Infarction	Cisplatin (day-1, 60mg/m2), Etoposide (Day1-3, 100 mg/m²) per 4 weeks	During day two of chemotherapy cycle 3	Endoluminal brachytherapy four months before chemotherapy, total dose 14 Gy in 2 fractions	Smoking (for 20 years), hypertension, post-myocardial infarction (CABG)	Yes (Minor specific ST-T wave changes)	Chemotherapy was discontinued / sublingual NTG, β-blockers, ACE-inhibitors, aspirin	Improved
Hazam et al, 2020 (9)	68, male	Lung Cancer (Type?) Stage IV (cT2N0M1)	Myocardial Infarction	Gemcitabine (2,280 mg) and Vinorelbine (57 mg)	Five days after chemotherapy cycle 1	None	DM type 2, hypertension, chronic kidney disease, peripheral artery disease	None	Chemotherapy was continued until cycle 3 / Aspirin,clopidogrel, metoprolol, simvastatin, heparin	Died four days after cycle three chemotherapy

...continuation Table 2. Characteristics of case reports included in this review

Author, Year	Age (years), Gender	Types of Lung Cancer	Cardiovascular Side Effects	Chemotherapy Regimen (Dose)	Onset	Radiotherapy	Cardiovascular Risk Factors	Initial Cardiovascular Examination (Baseline)	Therapy on Follow-up	Outcomes
King et al., 2013 (10)	55, male	Small Cell Carcinoma	Paroxysmal Supra-ventricular Tachycardia	Cisplatin (62 mg) and Etoposide (165 mg)	On Cisplatin chemotherapy, cycle 2	None	None	Yes (Normal)	Chemotherapy was continued by administering Bisoprolol 5 mg in the next cycle of chemotherapy.	Improved
Inanc et al., 2012 (11)	55, male	Non-Small Cell Carcinoma (Bone and Lymph node metastases)	Acute Pericarditis	Cisplatin (H1, 75mg/^{2}), Docetaxel (H1, 75mg/m^2), 5FU (H1-5, 750 mg/m^2)	Day 4 of cycle one chemotherapy	None	None	None	Chemotherapy was discontinued ISDN and IV Nitrate did not improve	Improved after chemotherapy was stopped
Katta et al., 2018 (12)	62, male	Small Cell Carcinoma	Myocardial Infarction	Cisplatin (day 1, 200 mg/m^2), Etoposide (day 1-3,100mg/m^2)	After 2nd cycle of chemotherapy	None	Hypertension (for 20 years), smoking (2 for five years)	None	Aspirin, clopidogrel, atorvastatin, nitrates, prazosin	Improved
Rao et al., 2015 (13)	55, male	Small Cell Carcinoma	Myocardial Infarction	Cisdplatin, Etoposide (every three weeks)	After two cycles of chemotherapy, 31 radiotherapy fractions	Concurrent radiotherapy 45 Gy (25 times), 20 Gy (10 times)	Smoking (for 30 years)	Yes (Normal)	Chemotherapy was stopped and radiotherapy was continued with cardiac adjustment doses.	Improved
Barony, 2011 (14)	Types of Lung Cancer Non-Small Cell	Adenocarcinoma	Kounis Syndrome	Carboplatin (450 mg), Paclitaxel	During Carboplatin cycle six, chemotherapy	None	Smoking	Yes (Normal)	NTG sublingual, methyl-prednisolone, aspirin	Improved (serum IgE Back to normal 180 kU/L)

Table 3. Results of Electrocardiography, echocardiography, coronary angiography, and laboratory examinations

Author, Year	Age (years), Gender	Electrocardiography	Echocardiography	Coronary Angiography	Laboratory findings
Zerna et al., 2014 (5)	70, male	T wave inversion Day 9 of treatment → ST elevation leads II, III, aVF, ST depression leads V2 and V3.	None	High-grade stenosis and thrombotic material in segment 2 of the right coronary artery	CK 1.13 μmol/L, CK-MB 6.60 μg/L, Myoglobin 279.90 μg/L, Troponin 350 ng/L
Oyakawa et al., 2017 (6)	59, female	None	Left ventricular dilatation (diastolic 67 mm), severe global hypokinetic decreased left ventricular EF (28%), normal left ventricular thickening, minimal pericardial effusion.	No coronary constriction	N-terminal pro-BNP 5286pg/ml Troponin T (13.7 ng/L), BNP (433 pg/ml)
Huang et al., 2022 (7)	69, male	PVC (bigemini and trigemini) and sinus bradycardia	None	None	Troponin and pro-BNP : normal
Bursac, 2018 (8)	58, male	ST elevation leads to aVR, diffuse ST depression on precordial leads	Inferolateral wall hypokinetic with mild systolic dysfunction and LV EF 50%	Multiple stenosis of the anterior interventricular branch of the left coronary artery	Troponin I 21.6 ng/mL Na+, K+, Ca2+, Mg2+ : normal
Hazam et al., 2020 (9)	68, male	ST depression leads to V3-V5	None	None	Troponin I 0.34 ng/mL, CK-MB 18 μg/L
King et al., 2013 (10)	55, male	Paroxysmal Supraventricular Tachycardia	Normal	None	Troponin Increase (0.9 ng/mL)
Inanc et al., 2012 (11)	55, male	ST elevation V2-V6, D1, D2 and aVL	Normal	Normal	Increased Troponin I (0.39 mg/dL)
Katta et al., 2018 (12)	62, male	Inversion of the T wave in the lateral leads	Left ventricular global hypokinetic. Mild left ventricular systolic dysfunction with LV EF 45% Mild mitral regurgitation	Single Vessel Disease (SVD) RAMUS ostioproximal complete occlusion, filling retrograde from grade II collaterals and branch vessel disease (diagonal total occlusion, filling retrograde from grade II collaterals)	CK-MB (1.4 → 6.6 mg/dL)
Rao et al., 2015 (13)	55, male	ST elevation leads V4-V6	Normal heart function with LV EF 65%	Normal, no stenosis	Troponin T, CK-MB, and Myoglobin: Normal
Barony, 2011 (14)	50, male	ST elevation leads II, III, AVF, and reciprocal ST depression V1-V3	None	None	Eosinophilia (5 %) Neutrophilia (75 %) Increased serum Ig-E (306kU/L)

during the next cycle of chemotherapy, another case died after chemotherapy was continued for up to 3 cycles); 1 case reported discontinuation of one chemotherapeutic agent (Cisplatin) and this patient showed improvement. The results of electrocardiography, echocardiography, angiography, and several laboratory parameters that support the diagnosis of cardiotoxicity in some cases are tabulated in Table 3.

DISCUSSION

Lung cancer is the most common cancer in men and the number four in women. Lung cancer is rare under the age of 40 years, and the incidence continues to increase until the age of 80 years (15). Clinically, lung cancer is divided into small cell carcinoma (SCC) and non-small cell carcinoma (NSCC). Non-small cell carcinoma is the most common type of lung cancer, accounting for 75-80 % of all cases (16).

Chemotherapy is recommended for patients with stage IV NSCC and a negative test result for the genetic variants EGFR, ALK, ROS1, METEx14, or BRAF; PD-L1 expression is less than 1 % and is contraindicated for PD-1 or PD-L1 inhibitors. Recommended chemotherapy regimens are based on performance status and include platinum agents (e.g. cisplatin, carboplatin), taxanes (e.g. paclitaxel, albumin-bound paclitaxel, docetaxel), vinorelbine, permetrexed etoposide, and gemcitabine (17).

Etoposide plus cisplatin is the most commonly used first-line combination chemotherapy regimen for patients with limited-stage SCC. For many years, platinum plus etoposide has been recommended for patients with extensive-stage SCC, with a preference for carboplatin over cisplatin because of its equivalent efficacy and more tolerable toxicity profile. However, the preferred regimen for extensive-stage SCC now includes (PD-L1) Immune checkpoint inhibitors, durvalumab or atezolizumab, plus platinum plus etoposide (18).

The most frequently referenced definition of cardiotoxicity is left ventricle (LV) impairment or failure due to chemotherapy. However, cardiotoxicity in relation to anticancer therapy can also be broadly defined as damage inflicted on the heart (functional or structural) from cancer treatments, including systemic anticancer therapy and radiotherapy. This includes cardiac dysfunction and effects beyond dysfunction, such as arrhythmias, hypertension, and thromboembolic events (19).

Several classes of chemotherapy are associated with an increased risk of cardiotoxicity, including anthracyclines, antimetabolites, alkylating agents, vinca alkaloids, and taxanes. Anthracyclines are the class of chemotherapy agents best known to cause cardiac dysfunction five times greater than non-anthracyclines (19).

Generally, two forms of chemotherapy-induced cardiotoxicity can be distinguished as (1) acute or subacute cardiotoxicity, found less frequently, can occur anytime from the start of chemotherapy up to 2 weeks after discontinuation of treatment. In this form, the most common clinical findings range from abnormalities in ventricular repolarization and changes in the QT-interval to supraventricular and ventricular arrhythmias or acute coronary syndromes, acute heart failure, and pericarditis or myocarditis-like syndromes; (2) chronic cardiotoxicity, the most frequent cumulative dose-dependent form, may be differentiated into two subtypes based on the time of onset of clinical symptoms: early, within one year of stopping chemotherapy and late after one year. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction that leads to severe congestive cardiomyopathy and may, in turn, ultimately lead to death.

Due to the low number of prevalent studies, the mechanisms of cisplatin-induced cardiotoxicity still need to be clarified. Jakubowski and Kemeny reported that cardiotoxicity occurs in 6 % of the patients receiving cisplatin and 5-FU (20). As stated in different literature, certain cardiotoxic manifestations of Cisplatin chemotherapy, including Cisplatin-induced angina, heart failure, thromboembolic events, acute myocardial infarction, autonomic cardiovascular dysfunction, hypertension, hypotension, pericarditis, myocarditis, and congestive cardiomyopathy (4). Hu et al. diagnosed a case of cervical squamous cell carcinoma in a 53-year-old woman. She was administered cisplatin (37 mg/m^2/wk) for

three weeks, but the left ventricular ejection fraction (LVEF) declined from 70 % to 48 % which confirmed that cardiac toxicity could be associated with cisplatin administration. The electrocardiogram (ECG) reveals a first-degree atrioventricular (AV) block and ST-segment depression of 0.05 mv in leads II, III, and V3-5. Neither cardiac markers nor N-terminal pro-B-type natriuretic peptide (NT-pro BNP) was elevated. Since careful physical examination and laboratory investigation confirmed that cervical cancer did not progress, and no other cause was evident, it was stated that the figured cardiotoxicity might be induced by cisplatin (21).

Cardiac toxicity is consistent with cisplatin therapy. Cardiotoxicity causes leakage of cardiac myocytes lactate dehydrogenase and creatine kinase (CK). This could be a secondary process resulting from lipid peroxidation induced by cisplatin or cardiac membranes (21). Cisplatin induces changes in electrolyte balance, particularly intracellular and extracellular potassium and magnesium concentrations. Such electrolyte imbalances are likely to play an important role in the pathogenesis of cisplatin-induced arrhythmia (10). In the case of lung cancer reported by Fassio et al., it was shown that supraventricular tachycardia (SVT) after chemotherapy administration (22) was associated with a combined regimen of Cisplatin and Etoposide. Few strategies have been proposed to prevent and treat cisplatin-induced cardiotoxicity effectively. Firstly, the echocardiography and ECG of the patient should be dynamically monitored before and during the therapy. Secondly, stop the usage of cisplatin at a relatively early stage. Thirdly, coenzyme Q10 and trimetazidine are used to prevent cardiac function from deterioration, based on potential pathophysiological mechanisms of cisplatin-induced cardiotoxicity (21). This experience might provide an example of time management for the use of medications for cardioprotection following cisplatin-induced cardiotoxicity.

Vinca alkaloids have been reported to cause autonomic neuropathy, angina with ECG changes, and, most commonly, myocardial infarction. The onset of myocardial infarction can range from a few hours to 3 days after the first or subsequent doses of vinca alkaloids. The exact mechanism by which vinca alkaloids cause cardiotoxicity is still unknown for certain. They may cause changes in preexisting atherosclerotic coronary vessels or anoxic myocardium and precipitate acute myocardial infarction. Others suggest that these agents can directly affect myocardial cells and increase their sensitivity to hypoxia, leading to myocardial infarction (23,25).

A recent review of 23 cases of various types of cancer receiving gemcitabine chemotherapy reported the association between gemcitabine treatment and potentially lethal cardiovascular drug side effects, including myocardial infarction, pericardial disease, supraventricular arrhythmias, and heart failure (24). A previous report on 979 patients treated with gemcitabine in 22 phase-2 trials demonstrated the incidence of myocardial infarction (0.5 %), heart failure (0.4 %), arrhythmia (0.2 %), and pericarditis (0.1 %), respectively (24). Similar to fluoropyrimidines (another antimetabolite), vasospasm is thought to be responsible for gemcitabine-associated myocardial infarction (24).

The incidence of various paclitaxel-related adverse cardiovascular reactions has been demonstrated in more than 3400 patients treated with paclitaxel. Data were obtained from various sources, including The Cancer Therapy Evaluation Programs (CTEPs), the Adverse Drug Reaction database, and different clinical trials involving paclitaxel. An incidence of 0.5 % of all adverse (life-threatening reactions and death) grade 4 and 5 cardiac events was found from CTEP. The incidence of ventricular tachycardia (VT) and ventricular fibrillation (VF) is reported to be 0.26 %; significant atrial arrhythmia (atrial fibrillation, palpitations, supraventricular tachycardia) 0.24 %; heart block 0.11 %; and ischemic events grades 4 and 5 as 0.29 % (23).

The cardiotoxicity of a chemotherapy agent depends on different factors related to the regimen itself and the individual patient. Understanding these factors may be relevant to reducing the occurrence or severity of cardiovascular side effects. The dose of chemotherapy administered during each session, the cumulative dose, the dosing schedule, the route of administration, the combination of drugs given, and the order in which these drugs are given are some important drug-related factors to consider. Recent

evidence showed that the patient-related factors associated with cardiotoxicity are age, previous cardiovascular disease, radiation therapy, metabolic abnormalities, and hypersensitivity to the regimen. Recognizing the risk factors for cardiotoxicity may be of clinical importance to prevent and reduce the side effects (25).

Thoracic radiotherapy, as the most important component of concurrent chemo-radiotherapy, is potentially associated with cardiotoxicity, which has long been known in patients with breast cancer or Hodgkin's lymphoma (26). The clinical relevance of this manifestation in patients with advanced lung cancer is unclear, and data regarding thoracic radiotherapy-induced cardiac toxicity in patient populations with SCC and NSCC are limited. This happened due to the low survival rate in the long-term period, as most of the symptoms usually occur with a long latency time, as well as because of the poor prognosis of these patients (27). Patients with lung cancer are more likely to have harmful comorbidities such as advanced age and smoking. They may receive higher doses of cardiac radiation, thus predisposing them to earlier cardiovascular events. In addition, the concomitant use of platinum-based chemotherapy may increase the risk of cardiotoxicity (26).

The retrospective cohort study of Chen et al., which included 128 NSCC patients who received concurrent platinum-based chemoradiotherapy (platinum/taxol), stated that right ventricle-free wall longitudinal strain (RV-FWLS) and right ventricle-global longitudinal strain (RV-GLS), the parameters for RV systolic function, were significantly reduced six months after concurrent chemoradiotherapy (26).

Hatakenaka et al. found that platinum-based concurrent chemoradiotherapy for esophageal cancer impairs cardiac function from the early treatment stage, and this impairment was prominent in the high radiation dose group. The multifactorial pathophysiology includes procoagulants and direct endothelial toxic effects (28). Haugnes et al. reported that testicular cancer survivors treated with platinum had unfavorable cardiovascular risk status and a higher incidence of cardiovascular events. Platinum-based therapy also increases the risk of thrombus formation (29).

This review reports various chemotherapy regimens, i.e. cisplatin, pemetrexed, etoposide, gemcitabine, docetaxel, vinorelbine, carboplatin, and paclitaxel. These regimens are associated with diverse potential mechanisms of chemotherapy-induced cardiotoxicity. Cardiotoxic effects attributed to Cisplatin (platinum-based agents) have been documented in a range of cases, encompassing diverse toxicities such as hypertension, coronary artery disease, arrhythmias, and heart failure.

Cisplatin, etoposide, gemcitabine, docetaxel, vinorelbine, and carboplatin have the capacity to directly harm myocardial cells, leading to cardiomyopathy and heart failure [30]. Paclitaxel, on the other hand, is known to induce cardiac ischemia, which can result in myocardial infarction and heart failure (30). Cisplatin's interaction with copper transporters can reduce cellular accumulation of Pt-compounds, potentially leading to chemotherapy resistance (31). Pemetrexed is linked to a low incidence of cardiotoxicity (30), although it can cause pericarditis (32). Gemcitabine's interaction with other chemotherapy agents, like vinorelbine, can augment the area-under-the-curve and maximum concentration of gemcitabine ([30). Further, Carboplatin is also associated with pericarditis (32).

As mention previously, the mechanism behind Cisplatin-induced cardiotoxicity involves both direct harm to cardiomyocytes and the generation of reactive oxygen species (ROS), leading to inflammation and the formation of blood clots (33). Cardiac toxicity linked to cisplatin therapy often caused by the release of cardiac myocyte enzymes, including lactate dehydrogenase and creatine kinase. This phenomenon may result from a secondary process triggered by cisplatin-induced lipid peroxidation affecting cardiac membranes (21). Cisplatin is known to induce imbalances in electrolyte levels, particularly impacting the intracellular and extracellular concentrations of potassium and magnesium. These electrolyte disturbances are believed to play a significant role in the development of cisplatin-induced arrhythmias (10). It is important to note that potential cardioprotective therapies should be considered. ACE inhibitors, beta-blockers, and dexrazoxane have demonstrated their efficacy

in reducing the risk of chemotherapy-induced cardiotoxicity (34).

Both the European Society of Cardiology (ESC) and the European Society of Medical Oncology (ESMO) provided guidelines for managing patients receiving potentially cardiotoxic agents. Before starting any potentially cardiotoxic agent, all patients should undergo a thorough cardiovascular assessment, with a particular focus on a history of ischemic disease or impaired cardiac function. Blood pressure should be measured, and in patients receiving multitarget agents, this and other co-morbidities should be managed appropriately before and during therapy. Basic investigations should include an ECG, assessment of left ventricular ejection fraction (LVEF), and measurement of cardiac biomarkers (troponins and BNP, or NT ProBNP) (19). To detect cardiac damage, the adopted diagnostic approach is the estimation of left ventricular ejection fraction by echocardiography. This approach shows low sensitivity toward early prediction of cardiomyopathy when the possibilities of appropriate treatments could still improve the patient's outcome. Cardiac troponins, however, show high diagnostic efficacy as early as 3 months before the clinical onset of cardiomyopathy. The increase in their concentrations is correlated with disease severity and may predict the new onset of major cardiac events during follow-up. Negative troponin concentrations may identify patients with a very low risk of cardiomyopathy (negative predictive value, 99 %). Concerning cardiac natriuretic peptides, definitive evidence in regard to a diagnostic or prognostic role in predicting chemotherapy-induced cardiomyopathy is still lacking (35).

Wu et al. (2023) based on the concept that radiotherapy (RT) can provoke a systemic immune response, which gives a strong rationale for the combination of RT and immune checkpoint inhibitors (ICIs), and that RT is a double-edged sword that not only enhances systemic antitumor immune response but also promotes immunosuppression to some extent, performed a systematic review and meta-analysis to assess the safety and efficacy of RT/chemoradiotherapy (CRT) and ICI combination therapy for non-small cell lung cancer (NSCLC) patients. 3,652 articles were identified for screening and 25 trials containing 1,645 NSCLC patients were identified. For stage II-III NSCLC, the one- and two-year overall survival (OS) was 83.25 % and 66.16 %, respectively. For stage IV NSCLC, the one and two-year OS was 50 % and 25 %. However, the incidence of cardiotoxicity (0 %-5.00 %) was low, but it was associated with a high mortality rate (0 %-2.56 %). Adverse reactions accounted for 0 %-2.7 %, with the most common effects including acute coronary syndrome (2.5 %), heart failure (2.5 %), atrial fibrillation (0 %-2.70 %), and myocardial infarction (0.21 %-2.56 %). Adverse reactions observed during the trials were: myocardial infarction (0.21 %-2.56 %), cardiac arrest (0.42 %), cardiomyopathy (0.21 %), cardiopulmonary failure (0.21 %), aortic dissection (0.21 %) and right ventricular failure (0.21 %). It was identified that myocardial infarction was an adverse event associated with the highest risk of mortality (36).

Cardiovascular diseases (CVD) represent a clinically important but mechanistically understudied complication that interferes with the continuation of best-possible care, induces life-threatening risks, and/or leads to long-term morbidity. These concerns are exacerbated by the fact that targeted therapies and immunotherapies are frequently combined with radiotherapy, which induces durable inflammatory and immunogenic responses, thereby providing a fertile ground for the development of CVDs. Stressed and dying irradiated cells produce 'danger' signals including, but not limited to, major histocompatibility complexes, cell-adhesion molecules, proinflammatory cytokines, and damage-associated molecular patterns. These factors activate intercellular signaling pathways, which potentially have detrimental effects on heart tissue homeostasis. Evidence indicates that the secretome of irradiated tumors entails factors that exert systemic, remote effects on the cardiac tissue, potentially predisposing it to CVDs. Thus, it is suggested that diverse disciplines can utilize pertinent state-of-the-art methods in feasible experimental workflows to shed light on the molecular mechanisms of radiotherapy-related cardiotoxicity at the organismal level and untangle the desirable immunogenic properties of cancer therapies from their detrimental effects on heart

tissue. The results of such highly collaborative efforts hold promise to be translated to next-generation regimens that maximize tumor control, minimize cardiovascular complications, and support quality of life in cancer survivors (37).

CONCLUSIONS

Most advanced lung cancer patients with chemotherapy-related cardiotoxicity are males with age above 50 years. The most relevant cardiotoxicity is myocardial infarction, with most chemotherapy regimens platinum-based, a combination of Cisplatin and Etoposide. The majority of cases showed promising results after discontinuing chemotherapeutic agents suspected to be related to cardiotoxicity. Early detection of patients with cardiovascular risk before determining the appropriate chemotherapy regimen and further routine check-ups both during and after chemotherapy could be influential in reducing morbidity and mortality related to cardiotoxicity.

Authors' contributions

MZ and ID made the initial conception and idea. MZ, SAS, and AQ performed literature searching and prepared the initial manuscript. AQ made manuscript revisions. MZ and ID reviewed and advised for critical revisions. All contributing authors approved the final draft.

Competing interests

The authors declare no competing interests.

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