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Cardio-oncology (MG Fradley, Section Editor)

Cardiovascular Complications Associated with Contemporary Lung Cancer Treatments

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Opinion statement

Lung cancer is the most common form of cancer in humans and the leading cause of cancer-related death worldwide. Traditionally, lung cancer has been diagnosed as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). However, recent developments in molecular pathology have revolutionized the diagnosis and treatment of the disease, thus improving patient prognosis and increasing the number of survivors. In advanced NSCLC cases, molecularly targeted drugs for patients with positive driver gene mutation/rearrangement, and immune checkpoint inhibitors for those with a positive biomarker, have changed the standard of care. SCLC is a highly malignant entity. In addition to the chemotherapy and radiotherapy, immune checkpoint inhibitors have recently provided some hope for extended-stage SCLC. Smoking cessation is related to decreased morbidity. However, early metastasis remains a significant challenge. Recently, cancer therapy–related cardiovascular disease (CTRCD) has emerged as diverse pathophysiology, including fulminant myocarditis, fatal arrhythmia, pericarditis, hypertension, and thrombosis, that emerged with modern lung cancer therapies. Cardio-oncology is a new

interdisciplinary collaboration to develop methodologies to manage cardiovascular risk factors and CTRCDs with the common goal of minimizing unnecessary interruption of cancer treatment and maximizing outcomes of lung cancer survivors.

Introduction

Lung cancer is one of the most common forms of cancer in humans and the leading cause of cancer-related death worldwide, affecting about 2 million people, with 1.6 million deaths each year [1].

Treatment options include surgery, radiation therapy, and drug therapy (Fig. 1), and are selected depending on histology, stage, and performance status [2]. Traditionally, patients diagnosed with lung cancer are classified as small cell lung cancer (SCLC) (~ 15%) [3, 4] and non-small cell lung cancer (NSCLC) (~ 85%) [5, 6•], while NSCLC is further subdivided into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. For early-stage NSCLC, surgery remains the recommended treatment, with obtained resection specimens used for pathological staging for NSCLC. In contrast, clinical staging for SCLC and advanced NSCLC is limited to biopsy samples and imaging.

In patients with advanced NSCLC, a dramatic revolution in diagnosis and treatment, driven by advances in molecular pathology, has led to an increase in the number of cancer survivors [5, 6•, 7•, 8, 9]. Molecularly targeted therapies have become standard care for patients with positive driver genes. Also, the use of immune checkpoint inhibitors has been shown to provide significant improvements as compared to chemotherapy for advanced and driver-negative NSCLC [10–13].

SCLC is a highly malignant entity with a fast growth rate [14]. Although it is susceptible to chemotherapy

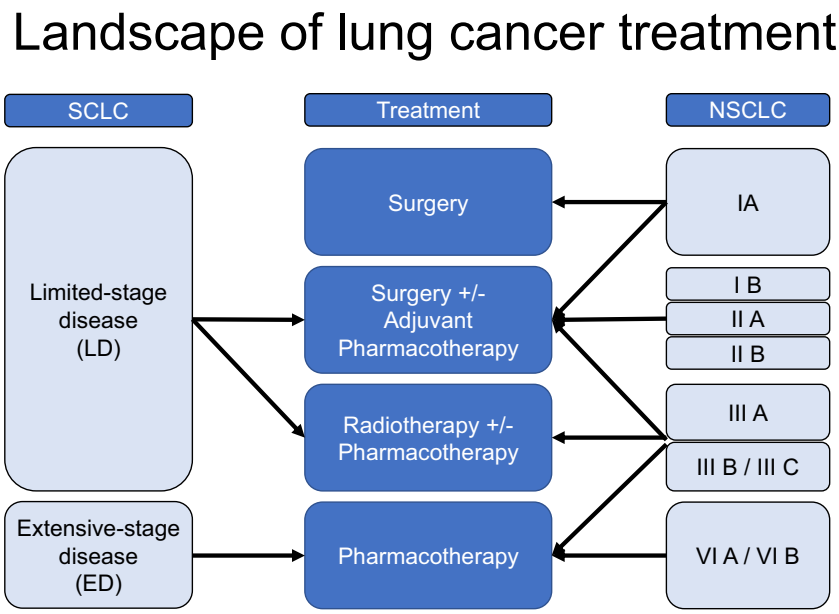

Fig. 1. Landscape of lung cancer treatment. Treatment options for lung cancer include surgery, radiation therapy, and drug therapy and are selected depending on the histology, stage, and performance status. For early-stage NSCLC, surgery remains the recommended treatment. In patients with advanced NSCLC, advances in molecular pathology, targeted therapy, and immunotherapy have dramatically revolutionized the diagnosis and treatment. SCLC is a highly malignant entity with a fast growth rate. Although it is susceptible to chemotherapy and radiotherapy, early metastasis in the brain remains a significant challenge. Currently, mixed immunotherapy is under clinical evaluation. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

and radiotherapy, early metastasis in the brain remains a significant challenge [3]. Epidemiological studies have identified reduced incidence with smoking cessation. However, the mortality rate remained stagnant for nearly three decades [7•] until immune checkpoint inhibitors have improved OS [15•]. Currently, mixed immunotherapy, including combinations of radiotherapy, chemotherapy, or molecularly targeted therapy, is under clinical evaluation [15•].

Cancer therapy–related cardiovascular disease (CTRCD) (Table 1) is a pathophysiology that has emerged with the modern cancer therapies [16, 17•, 18•]. Cardiovascular disease (CVD) has been a major competing risk factor with effects on lung cancer patient outcomes [19, 20]. Both CVD and lung cancer have common risk factors, such as smoking and inflammation [21, 22]. In particular, preexisting CVD is associated with a poor prognosis for patients undergoing lung cancer treatment [23]. In addition to conventional cardiotoxicity associated with chemotherapy [24, 25] and radiation therapy [26, 27], heart failure, atrial fibrillation, myocarditis, venous thromboembolism, and hypertension with molecularly targeted therapy [28, 29], as well as the rare but fatal fulminant myocarditis associated with immune checkpoint inhibitors [30, 31], have emerged as critical unmet medical needs [32••].

Cardio-oncology is a new interdisciplinary collaboration [33, 34••] with the common goal of improving cancer care through prevention, diagnosis, and treatment of CTRCD [35]. There have been concerns that underdiagnosis of CTRCD leads to cardiovascular disease, while overdiagnosis exacerbates cancer [36, 37]. Therefore, there is an urgent need to develop new methodologies [38, 39] to establish evidence-based cardio-oncology clinical practice guidelines [40]. In the future, cardio-oncology rehabilitation [41, 42] is expected to become a pillar in lung cancer survivorship care.

This review will focus on the rapidly evolving lung cancer landscape and discuss challenges and opportunities with cardio-oncology.

Molecularly targeted therapy

Drug therapy for lung cancer has not achieved significant progress since the introduction of platinum-based agents in the 1970s [5, 8].

However, advances in molecular pathology led to revealing the overexpression of epidermal growth factor receptor (EGFR) in NSCLC [8], followed by the development of EGFR tyrosine kinase inhibitors (TKIs) [43]. Initially, ethnic differences were given as the reason for differences in the efficacy of TKIs between Western and East Asian countries. However, detailed studies showed a causal relationship with EGFR mutations [44, 45] and the era of precision medicine began [46–48].

Currently, molecularly targeted drugs are given as first-line treatment for most non-squamous cell cancers among NSCLC, with the most common driver mutations/metastases EGFR (15%) and ALK (5%), ROS1, MET, and BRAF [46–48].

With the widespread use of molecularly targeted therapies [6•], various CTRCDs that differ from traditional cardiovascular diseases [28, 29] have also become more relevant in regard to lung cancer [20, 19].

Epidermal growth factor receptor

EGFR is a widely expressed cell surface molecule known to be involved in cancer development and progression. The EGFR family consists of four structurally similar tyrosine kinase receptors: EGFR/ErbB1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4. Overexpression of EGFR has been associated with worse clinical outcomes in several different types of cancer, including NSCLC [8].

Table 1. Outline of cardiovascular complications associated with lung cancer therapies

		Arrhythmia	Heart failure	Arterial vascular disease	Venous thromboembolism	Pulmonary hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Molecularly targeted therapies	EGFR inhibitors	X	X	X	X				
	ALK inhibitors	X				X			
	BRAF inhibitors	X	X						
	MEK inhibitors	X	X			X			
	VEGF inhibitors		X	X	X		X		
	HER2 inhibitors		X						
Immune checkpoint inhibitors			X						
Conventional	chemotherapies				Platinum-based therapy			X	X
		X							
	Microtubule-binding agents (taxanes)	X		X					
Radiotherapy		X	X	X		X		X	X

Cancer treatment–related cardiovascular disease is emerging pathophysiology that is independent of traditional coronary risk factors. Cancer therapies range from minimal cardiotoxicity to extensive cardiovascular risk profiles. Note that safety concerns should be considered a class effect, not an individual agent unless head-to-head controlled trial data are available. *ALK*, anaplastic lymphoma kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; *EGF*, epidermal growth factor; *HER2*, human epidermal growth factor receptor 2; *VEGF*, vascular endothelial growth factor

EGFR-TKIs were among the first molecularly targeted therapies to receive approval for use in patients who would otherwise be scheduled for platinum-based chemotherapy [43]. Subsequently, EGFR mutations were found to be critical predictive markers of efficacy [44, 45]. EGFR-mutation-positive rates are higher in women, East Asians, and non-smokers, who account for approximately 15% of all individuals with advanced and/or metastatic NSCLC [49].

In patients with EGFR tumor mutations, EGFR-TKIs have been shown to improve progression-free survival (PFS) and overall survival (OS) as compared with platinum-based chemotherapy, making them a first-line treatment option. However, it has been found that many patients develop resistance to erlotinib, gefitinib, and afatinib after about 10 months of administration [6•]. On the other hand, osimertinib improves PFS and OS, and reduces central nervous system (CNS) metastasis in patients with NSCLC, including those with the T790M mutation in EGFR, which contributes to TKI resistance [50, 51].

Erlotinib is not associated with cardiovascular complications in several reports of NSCLC clinical trials. In a study that compared bevacizumab plus erlotinib versus erlotinib alone, only a single case with pulmonary embolism was observed in both groups [52]. In a clinical trial that compared erlotinib plus gemcitabine versus gemcitabine alone in pancreatic patients, there was a more significant number of coronary events, including myocardial infarction and thromboembolism in the erlotinib group [53].

Gefitinib has been suggested to be associated with an increased risk of acute coronary syndrome (ACS) due to its effect on platelet function [54]. However, based on the results of clinical trials, cardiovascular complications may not be a significant safety concern with its use [55].

Afatinib is an irreversible inhibitor of EGFR/ErbB1, HER2/ErbB2, and HER4/ErbB4, and inhibition of the HER2 receptor has raised concerns regarding the cardiological safety of this drug [56]. Clinically, the frequency of events in randomized trials has been shown to be comparable between afatinib and a placebo, and between afatinib and chemotherapy. However, a significant reduction in left ventricular ejection fraction (LVEF) was more common in the chemotherapy arm than in the afatinib arm. In contrast, the frequency of that reduction was similar in the afatinib and placebo arms [57].

Dacomitinib is a second-generation EGFR-TKI characterized by irreversible inhibition of HER1, HER2, and HER4 [58]. Its use was shown to significantly improve PFS as compared to gefitinib, a first-generation, selective, and reversible EGFR-TKI, when given as first-line treatment to EGFR-mutation-positive NSCLC patients in Japan and South Korea [59]. However, since HER2 inhibition is known to be correlated with heart failure, future clinical evaluations of its safety are warranted [60].

Osimertinib has been shown to be associated with cardiotoxicity, including QT prolongation, heart failure, and atrial fibrillation, in retrospective observational studies [61], while QT prolongation has also been reported in clinical trials [50]. In a meta-analysis, the percentage of cases of QT prolongation with osimertinib treatment was approximately 2% [62], and other studies have noted QT prolongation and reduced LVEF in patients treated with this drug [51]. It has been speculated that osimertinib inhibits HER2 receptors, leading to acute heart failure [63].

It should be noted that safety concerns may be a class effect of EGFR-TKIs. Also, discontinuation of EGFR-targeted therapy can accelerate cancer

progression [64]. Therefore, any decision to discontinue EGFR-TKI administration must be carefully considered, especially in cases of metastatic disease [65].

Anaplastic lymphoma kinase

Oncogenic gene fusions of ALK leading to triggering of abnormal dimerization and activation have been found in approximately 5% of metastatic NSCLC cases [66–68]. Furthermore, patients with ALK rearrangements have a three to five times greater incidence of VTE as compared to the general NSCLC population [69].

Crizotinib, an oral ATP-competitive inhibitor of the ALK and MET receptor tyrosine kinase, is the first agent shown to have efficacy in patients with ALK-positive NSCLC [70, 71]. Although second- (alectinib, brigatinib, ceritinib) [72–74] and third- (lorlatinib) [75] generation ALK-TKIs have been shown to have more specific kinase inhibition, and are also effective for crizotinib-resistant patients, drug resistance remains a challenge for patients with ALK rearrangements [6•].

Two types of adverse cardiac events, bradycardia and prolonged QT interval, have been reported in relation to this class of TKI [20, 19].

In vitro toxicity studies of crizotinib with human cardiomyocytes have shown increased reactive oxygen species (ROS), caspase activation, cholesterol accumulation, cardiomyocyte function disruption, and blockade of hyperpolarization-activated cyclic nucleotide channel 4 (HCN4). While most events were mild, symptomatic bradycardia cases (e.g., syncope, dizziness, hypotension) were occasionally noted. HR reduction with crizotinib may appear within several weeks after initiation of therapy [76–78].

Regulatory authorities have highlighted precautions for the use of this class of TKIs, including administration of other drugs known to cause bradycardia or electrolyte abnormalities and concomitant use of drugs known to prolong the QTc interval. Routine evaluations of HR and BP, as well as ECG and serum electrolytes, are recommended for patients with ALK-rearrangement during treatment [20, 19].

ROS1: proto-oncogene receptor tyrosine kinase

Approximately 1% of patients with NSCLC have chromosomal rearrangement of the ROS1 gene [78].

Although ALK and ROS1 share the same structural homology, not all ALK-TKIs are effective for NSCLC patients with ROS1-rearrangement [6•].

Crizotinib is one of the first ALK-TKIs to be proven effective for ROS1-positive NSCLC [79], though bradycardia and QT prolongation have been reported in clinical trials.

Entrectinib, an orally available TKI given for TrkA, TrkB, TrkC, and ROS1, can cross the blood-brain barrier, and was recently approved based on efficacy and tolerability shown in patients with ROS1 or TRK-positive NSCLC [80]. This drug appears to be the most suitable treatment for TKI-naive patients, especially those presented with brain metastasis. Conversely, treatment may not be successful in cases of systemic progression with acquired resistance mutations. Precautions for use include cardiac disorders, such as heart failure, ventricular extrasystoles, and myocarditis, thus close monitoring of patient condition before and during administration, including cardiac function (electrocardiogram, echocardiogram) and creatine kinase testing, as appropriate [81].

BRAF: V-raf murine sarcoma viral oncogene homolog B

BRAF mutations have been found in 1 to 2% of patients with lung adenocarcinoma. BRAF mutations include V600E, G469A/V, K601E, and L597R, among which the V600E mutation is known to be involved in carcinogenesis through activation of the MAPK pathway BRAF mutations have been reported in solid tumors such as melanoma, papillary thyroid cancer, colorectal cancer, and ovarian cancer as well as NSCLC. More than 85% of BRAF mutation-positive lung cancers are adenocarcinomas [82]. When treatments with a single-agent BRAF inhibitor, dabrafenib or vemurafenib, fail, combined pathway blockade using a BRAF inhibitor (dabrafenib) and MEK inhibitor (trametinib) can be attempted in patients with metastatic *BRAF* V600E-mutant NSCLC [83].

Cardiotoxicity associated with the combination includes decreased left ventricular ejection fraction (LVEF), heart failure, QTc prolongation, hypertension, and thromboembolism. In a study of malignant melanoma, heart failure occurred in 8.1% (RR 3.7 compared to BRAF alone), hypertension in 19.5% (RR 1.49), and pulmonary embolism in 2.2% (RR 4.4) of patients. Therefore, cardiotoxicity may be due to the combination of BRAF inhibitor and MEK inhibitor, not BRAF inhibitor alone [84].

Clinically significant effects on the QTc interval have been reported with vemurafenib, a selective BRAF inhibitor. On the other hand, dabrafenib, a recently approved BRAF inhibitor, appears to affect the QTc interval when used in combination with trametinib [85]. In an open-label, multicenter safety study of patients with metastatic melanoma who had received at least one dose of vemurafenib, grade 1 and 2 QT interval prolongation occurred in 9%, and grade 3 and 4 QT interval prolongation occurred in 2% [86].

The mechanisms of cardiotoxicity include induction of oxidative stress and apoptosis in cardiomyocytes by inhibition of the MAPK signaling cascade and elevation of blood pressure and thromboembolism by inhibition of angiogenesis. Approved indications recommend baseline assessment of cardiovascular risk factors and cardiovascular monitoring during treatment to prevent cardiotoxicity [87, 88].

Neurotrophic receptor tyrosine kinase

The NTRK genes NTRK1, NTRK2, and NTRK3 encode the tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, respectively. Mutations in the NTRK gene have been identified in less than 1% of examined NSCLC tumors [89].

Larotrectinib, an NTRK inhibitor, has been evaluated in clinical trials of cancer patients with NTRK gene rearrangements, including those with lung cancer, and shown to improve tumor response and 12-month PFS [90]. It is one of the first drugs approved for the treatment of cancers with more than one target gene, regardless of primary site [91]. Risk-benefit assessment is ongoing, including cardiovascular adverse events such as QT prolongation [92].

Vascular endothelial growth factor

Angiogenesis is one of the hallmarks of cancer, and an increased level of VEGF is associated with increased risk of recurrence, metastasis, and death in most types of tumors that develop in humans, including NSCLC. Because VEGF stimulates endothelial cell proliferation, improves survival, and increases vascular integrity, VEGF inhibitors may lead to endothelial dysfunction [93].

Bevacizumab, a humanized anti-VEGF monoclonal antibody, has been proven to be effective to improve OS for metastatic NSCLC [94, 95]. Bevacizumab is still an option for NSCLC to be given in combination with chemotherapy, molecularly targeted agents, or immune checkpoint inhibitors [96, 97]. The most common cardiovascular complication of bevacizumab therapy is arterial hypertension, which develops in about one-third of treated patients [28]. However, hypertension associated with bevacizumab may be associated with better response to treatment as well as better prognosis. Therefore, it is crucial to continue anti-VGEF therapy by use of antihypertensive therapy and thorough blood pressure monitoring [98]. Other cardiovascular complications of bevacizumab therapy are cardiac dysfunction and thromboembolic events.

Ramucirumab is a monoclonal antibody that selectively targets VEGFR2; blocks signaling by VEGFA, VEGFC, and VEGFD in NSCLC; and shows a broad range of antitumor activity. The combination of ramucirumab and docetaxel has been found to be effective for treatment of patients with metastatic NSCLC whose disease has progressed after undergoing platinum-based chemotherapy. The combination of ramucirumab with different treatment regimens shows a favorable risk-benefit ratio in many cancer types, including NSCLC [99].

Nintedanib inhibits three different pathways associated with the activities of VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). In a study of the cardiovascular safety of nintedanib in patients with and without risk factors for atherosclerosis, cardiovascular events occurred at a similar frequency in the nintedanib and placebo groups. Also, the frequency of myocardial infarction was shown to be significantly increased in patients with risk factors [100].

Immunotherapy

The introduction of immune checkpoint inhibitors (ICIs) revolutionized OS for patients with metastatic/progressive NSCLC [6•] or extended-stage SCLC [15].

ICIs are monoclonal antibodies to programmed cell death-1 (PD-1), programmed cell death-ligand-1 (PD-L1), and cytotoxic T cell lymphocyte antigen-4 (CTLA-4), which act on T cells and antigen-presenting cells to promote destruction of cancer cells. Nivolumab and pembrolizumab target PD-1, atezolizumab and durvalumab inhibit PD-L1, and ipilimumab blocks CTLA-4. Indications for these agents continue to expand in malignancy and disease settings; thus, many previously standard therapies have been reshaped.

ICIs for NSCLC

PD-1 and PD-L1 therapies were evaluated for patients with NSCLC after initial treatment with platinum-based chemotherapy [12]. Subsequently, a series of first-line, adjuvant, and maintenance trials were conducted to evaluate the risks and benefits of immune checkpoint inhibitors. For many patients with NSCLC without an oncogenic driver gene mutation, ICI treatment, either alone or in combination with standard platinum doublet chemotherapy, has been moved from second-line to become a first-line therapy option [6•]. All patients with advanced lung cancer should undergo tissue evaluation for baseline PD-L1

expression. Additionally, other potential biomarkers, such as mutational load and tumor-infiltrating lymphocyte profiles, are presently under investigation [101].

ICIs for SCLC

Nearly 30 years following the introduction of platinum-based chemotherapy [3, 4, 7•], ICI therapy has finally been shown to improve OS in SCLC patients [102] and ICIs have been approved as first-line agents to treat extended-stage SCLC. As a first-line agent, addition of the anti-PD-L1 antibody atezolizumab to chemotherapy has been shown to improve OS. However, in relapsed patients, no significant improvement in OS was found to be achieved as compared to conventional chemotherapy. Additionally, PD-L1 expression was generally low or absent in SCLC, making it impossible to be used as a predictive biomarker. Blood-based measures of tumor mutational burden also had no predictive value. Therefore, there remains a need for further research to identify predictive biomarkers to optimize treatment strategies [15•].

Cardiovascular complications of ICIs

A variety of immune-related adverse events (irAEs) can occur during anti-PD1/anti-PDL1 therapy [103, 104]. Cardiovascular irAEs include myocarditis, vasculitis, ischemic episodes, arrhythmias, and pericardial disease [39].

Rare but fatal fulminant myocarditis should not be underestimated [31]. While the overall risk of fatal fulminant myocarditis seems to be low (< 1%), the incidence of ICI-related myocarditis is increasing in parallel with expanding indications for ICIs [30].

Clinical manifestations of ICI-associated myocarditis include signs of acute heart failure, which clinically manifests as chest pain, shortness of breath, pulmonary edema, and even cardiogenic shock. The degree of systolic dysfunction varies, and about half of patients do not have a decrease in ejection fraction [105].

Early data suggest an increased risk of arrhythmias, including heart block and atrial and ventricular arrhythmias causing syncope and sudden death [105].

ICI-associated myocarditis does not appear to be dose-dependent, and the timing of onset is difficult to predict. Most reports indicate that the onset of ICI-associated myocarditis occurs within 2 to 3 months, but some cases appear more than 3 to 6 months after therapy initiation. The risk factors for ICI-associated myocarditis are unknown. Caution is required in patients with cardiovascular risk factors and the increasing number of patients receiving combined immunotherapy with platinum, angiogenesis inhibitors, and radiation therapy.

Currently, recommendations for managing immune-related adverse events are based on consensus rather than evidence-based guidelines [105–107].

Diagnosis of ICI-associated cardiomyopathy relies on imaging, biomarkers, and electrocardiographic studies. Global longitudinal strain (GLS) and cardiac magnetic resonance imaging (MRI) help early diagnosis. The diagnosis can be confirmed by endomyocardial myocardial biopsy (EMB), but it may not be practical to perform this invasive test in all patients in a timely manner. ICI-associated myocarditis has been reported to be associated with myositis, pneumonia, hepatitis, and colitis. Therefore, the onset of other irAE may potentially be complicated by myocarditis.

Management of patients on ICI should include early diagnosis of myocarditis. When myocarditis becomes apparent, corticosteroids should be started immediately. Consult cardiologists in case of fatal arrhythmias or rapid deterioration of cardiac function. The treatment of steroid-refractory cases is not well established. Immunosuppressive agents such as infliximab, mycophenolate mofetil, and high-dose immunoglobulin may be effective. IL6 blockade (tocilizumab) may be considered in cases of cytokine release syndrome.

Cytotoxic chemotherapy

For advanced or metastatic NSCLC, platinum-based therapy has been used as first-line treatment since the 1970s, in combination with gemcitabine, taxane, or pemetrexed [5, 6•]. However, in recent years, there have been dramatic changes with the advent of molecularly targeted therapies and immune checkpoint inhibitors [7•, 8].

For SCLC treatment, chemotherapy has long been playing a central role. The combination of cisplatin and etoposide is given for extended-stage SCLC, and radiation therapy and chemotherapy are used for limited-stage cases [3, 4]. With the recent advent of immune checkpoint inhibitors, platinum-based therapies and their role are slowly but steadily changing [102].

Cisplatin

Cisplatin is known to demonstrate vascular toxicity by causing vascular endothelial damage and platelet dysfunction [18•]. Coronary angina, myocardial infarction, venous thromboembolism, hypertension, arrhythmia, cerebral infarction, and peripheral vascular disease have been reported in the acute stage, as well as in chronic stage cases after 10–20 years. Furthermore, electrolyte abnormalities such as hypomagnesemia and hypokalemia associated with cisplatin-induced renal damage are causative of arrhythmias [19]. Therefore, it is recommended that cisplatin be changed to carboplatin in patients who are elderly, have a history of vascular disease, or with impaired renal function [2].

Gemcitabine

Treatment with gemcitabine can lead to thromboembolic complications [17•], especially vascular complications including thrombotic microangiopathy [19]. In those with NSCLC, when the combination of cisplatin and gemcitabine was compared to cisplatin monotherapy, addition of gemcitabine resulted in greater efficacy for treatment of the disease, but also increased cardiac ischemia and arrhythmias [20].

Taxanes

Taxanes (paclitaxel, docetaxel) interfere with microtubule to inhibit cell division and replication. Paclitaxel is arrhythmogenic with bradycardia and atrioventricular conduction block, but these are usually asymptomatic [17•]. Taxane-induced arrhythmias can be acute (during infusion) or subacute (up to 14 days after treatment) in patients with NSCLC [19]. Furthermore, taxanes cause vascular endothelial damage, which has been associated with vasospasm; thrombosis; and, though rarely, myocardial infarction [18•].

Pemetrexed

Serious cardiovascular events attributed to pemetrexed, such as myocardial infarction, peripheral edema, cardiac arrhythmia, and transient ischemic attack (TIA), have only been infrequently reported [19]. Those events usually occurred in patients receiving that in combination with another cytotoxic drug or in those with a history of cardiovascular disease [2].

Radiotherapy

The role of radiotherapy (RT) in lung cancer is diverse, as it is given for curative purposes, as preoperative and postoperative treatment, or as palliative irradiation. When irradiating the lung, respiratory motion must be taken into consideration. In recent years, high-precision treatments such as intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy (SRT), and image-guided radiotherapy (IGRT) have improved in accuracy and quality.

Radiotherapy for NSCLC

The standard treatment for stage I–II NSCLC is surgical resection. However, radiotherapy is the treatment of choice when surgery is not possible for medical reasons, such as the presence of smoking-related cardiovascular or respiratory complications [108, 109].

Stage III NSCLC includes a variety of pathologies. Patients who undergo radiotherapy alone have a poor prognosis, whereas subsequently established chemoradiotherapy has improved OS. Recently, consolidation immune checkpoint inhibitor therapy following concurrent chemoradiotherapy has prolonged PFS and OS [110].

Radiotherapy for SCLC

For SCLC patients with extensive-stage disease, whole-brain radiotherapy is indicated for those with brain metastasis. However, thoracic radiation therapy is not recommended for routine use [3, 4].

For limited-stage SCLC, twice-daily thoracic radiation therapy given concurrently with first or second cycle chemotherapy with etoposide and cisplatin has proven to be superior to sequential radiation therapy [3, 4].

Cardiovascular complications of radiotherapy

The cardiotoxicity of radiotherapy has led to treatment focus on cases with scant preexisting disease and good long-term survival, such as breast cancer and Hodgkin lymphoma. Radiation-induced pericarditis develops during or several months after treatment. Late effects, which can develop years or even decades after irradiation, include cardiomyopathy, coronary artery disease, valvular heart disease, conduction system abnormalities and arrhythmias, autonomic dysfunction, and vascular changes [26, 27].

Cardiac doses have been high in patients with locally advanced NSCLC to avoid the dose-limiting toxicity of fatal acute esophagitis and radiation pneumonitis [111]. Recently, the life expectancy of patients with locally advanced NSCLC has rapidly improved, and cardiac dose is known to be associated with both clinically significant cardiac toxicity and OS [112, 113]. Therefore,

radiation dose and radiotherapy coverage should be minimized to prevent cardiotoxicity even in patients with thoracic malignancy [111].

Surgery and other considerations

Cardiovascular complications of lung cancer treatment are not solely due to drug therapy. For example, venous thromboembolism (VTE) and atrial fibrillation (AF) are frequent comorbidities seen in perioperative lung cancer patients.

There are rare but potentially life-threatening oncology emergencies, including deep-vein thrombosis, QT-prolongation, and myocarditis. Thus, cardiologists need to establish proactive collaborations rather than reactive ones to minimize unnecessary interruptions in cancer treatment and maximize the quality of life and life expectancy of cancer patients [35].

Atrial fibrillation

AF is a common early postoperative complication seen in a variety of clinical settings. The incidence of AF after following thoracic surgery for lung cancer is high, and elevated preoperative NT-proBNP is known as a strong independent predictor of postoperative AF. While postoperative AF is often benign and transient, it has been shown to be associated with increased morbidity and mortality in cases that progress to heart failure and thromboembolism [114].

Venous thromboembolism

VTE is one of the major complications seen in patients diagnosed with lung cancer. Risk factors for related events in those cases consist of cancer-related (histology, stage), treatment-related (surgery, chemotherapy, antiangiogenic agents, supportive care agents), and patient-related (comorbidities, immobility, performance status, and history of thrombosis) factors [115].

Evidence-based clinical practice guidelines have been published for the risk-benefit assessment of secondary prevention (treatment of VTE) as well as primary prevention (lung cancer patients undergoing hospitalization, surgery, chemotherapy) of cancer-associated VTE [116].

Conclusion and future considerations

With the advent of an aging society, lung cancer incidence may exceed the preventive effect of smoking cessation.

Conventional treatments include surgery, radiation therapy, and drug therapy, which are determined based on histological type, stage, and performance status. Recently, molecularly targeted drugs and immune checkpoint inhibitors have revolutionized lung cancer diagnosis and treatment. New therapeutic approaches using combinations of molecular targeted therapy, angiogenesis inhibitors, cytotoxic chemotherapy, and immune checkpoint inhibitors have steadily been introduced to achieve long-term survival and better quality of life.

Cardio-oncology is a new interdisciplinary collaboration with the common goal of completing cancer treatment and improving cancer outcomes. In

addition to the competing risk of cardiovascular disease in lung cancer prognosis, the risk of cancer therapy–related cardiovascular disease has recently emerged. Especially, rare but life-threatening oncology emergencies, including pulmonary thromboembolism, torsades-de-pointes, and fulminant myocarditis, need proactive collaborations rather than reactive ones.

In the future, an essential need is for cardio-oncology rehabilitation that improves cardiorespiratory fitness before, during, and after lung cancer treatment in preparation for the rapidly increasing number of lung cancer survivors.

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Compliance with ethical standards

Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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