research article

Echocardiography and cardiac biomarkers in patients with non-small cell lung cancer treated with platinum-based chemotherapy

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Background. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and remains an important cause of cancer death worldwide. Platinum-based chemotherapy (PBC) for NSCLC can modify outcome while the risk of cardiotoxicity remains poorly researched. We aimed to evaluate the incidence and severity of cardiac injury during PBC in patients with NSCLC and to identify patients at risk.

Methods. This was a single-centre, prospective, observational study of patients with early and advanced stage NSCLC referred for PBC. In addition to standard care, patients were examined and evaluated for cardiotoxicity before the first dose (visit 1), at the last dose (visit 2) and 6 months after the last dose of PBC (visit 3). Cardiotoxicity (at visit 2 and 3) was defined as increase in the ultrasensitive troponin T, N-terminal pro-B type natriuretic peptide or decrease in left ventricular ejection fraction (LVEF).

Results. Overall, 41 patients (mean age 61 ± 9; 54% men; 68% advanced lung cancer) were included. The median number of PBC cycles was 4. During the study period, there were no incidents of heart failure, and 3 deaths caused by tumour progression were recorded. The mean values of biomarkers and LVEF did not change significantly ($p > 0.20$). However, 10 (25%) had cardiotoxicity which was independently associated with a history of ischemic heart disease ($p = 0.026$).

Conclusions. In NSCLC, cardiac assessment and lifestyle modifications may be pursued in patients with a history of cardiac disease and in patients with longer life expectancy.

Key words: cardiotoxicity; platinum-based chemotherapy; lung cancer; cardiac biomarkers

Introduction

Currently, lung cancer is not only the leading cause of cancer-related deaths, but is also the most frequently diagnosed cancer worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers. According to recent guidelines, platinum-based doublet chemotherapy is used as first line therapy in NSCLC. In addition to platinum agents (cisplatin or carboplatin), gemcitabine, pemetrexed, vinorelbine or a taxane is used.[2-4]

Cancer chemotherapeutic drugs, particularly anthracyclines, monoclonal antibodies and targeted drugs such as multiple tyrosine kinase inhibitors can induce cardiac damage.[5] In general, chemotherapy can cause cardiac damage by specifically targeting receptors on cardiomyocytes or by inducing oxidative stress, as shown in trastuzumab or anthracycline-induced cardiotoxicity, respectively.[6,7] Screening of patients before treatment and monitoring cardiac function during therapy has traditionally relied on left ventricular ejection

fraction (LVEF).[6] However, because assessment of LVEF lacks the sensitivity needed for detecting early subclinical changes, newer and more sensitive metrics of cardiotoxicity are needed. The most commonly used biomarkers to detect subclinical cardiac toxicity are cardiac troponins and atrial or B-type natriuretic peptides. Cardiac troponins reflect cardiomyocyte injury or death, whereas natriuretic peptides are released due to cardiac stretch and strain during congestive heart failure.[8,9]

In addition to the risk of cardiotoxicity related to specific anti-cancer therapy, cancer patients are at increased risk of cardiovascular (CV) disease due to older age and shared lifestyle risk factors (*e.g.*, smoking and obesity). With the introduction of new treatment modalities, the life expectancy of many cancer patients has improved substantially, and treatment-related comorbidities have become an important issue for cancer survivors. Cancer patients with longer life expectancy (childhood cancer, breast, prostate and colorectal carcinoma) are already more likely to die from CV disease than any other cause.[10] In addition, for NSCLC, new developments such as targeted therapies are showing potential for longer survival, and detection of early cardiac injury is becoming crucial for these patients.

Data regarding cardiotoxicity following platinum-based chemotherapy are scarce. There have been several studies reporting CV events and induced cardiotoxicity in animals following platinum-based chemotherapy.[11-17] Studies evaluating the long term effects of platinum-based chemotherapy in testicular cancer have shown a higher rate of CV events such as decreased LVEF and higher mortality due to CV disease in patients exposed to platinum-based regimens.[18-20] In addition, a large retrospective study showed that patients with NSCLC treated with chemotherapy and radiotherapy were more likely to develop heart failure as well as cardiac dysfunction.[21] To our knowledge, there has been only one prospective study of patients with NSCLC that evaluated cisplatin and anthracycline-based cardiotoxicity, and that study found no significant decrease in LVEF after treatment with cisplatin.[22]

Even though some degree of cardiac damage has been shown following treatment with platinum agents, it is still unclear whether platinum-based chemotherapy induces cardiotoxicity in patients with NSCLC. Hence, our aims were to evaluate cardiac function with echocardiography and biomarkers in patients with NSCLC treated with platinum-based chemotherapy and to identify those at risk for cardiotoxicity.

Patients and methods

Study design and patients

This was a single-centre, prospective, observational study. All patients with NSCLC who were referred for platinum-based chemotherapy in our clinic between June 2012 and September 2013 were screened to include those with early and advanced stage NSCLC treated with platinum-based doublets as adjuvant or metastatic therapy. Patients with adjuvant radiotherapy or concomitant chemoradiotherapy were not included in the study. Platinum doublets with vinorelbine, gemcitabine or pemetrexed were given according to guidelines and established clinical practice.[2,3] Cisplatin 80 mg/m^2 and carboplatin AUC 5 were used and modified according to the standard practice toxicity guidelines. Patients with a history, symptoms or signs of heart disease, or renal disease received carboplatin, while others received cisplatin. In addition to standard examinations, patients had evaluation of cardiac function by echocardiography and biomarkers before the first (visit 1), last cycle of chemotherapy (visit 2) and 6 months after completion of platinum-based chemotherapy (visit 3). Between visit 2 and visit 3, none of the patients was re-challenged with platinum-based chemotherapy. Physicians involved in the care of patients participating in the study were not aware of the results of biomarkers and echocardiography assessment, unless findings were pathological and would lead to a change in a patient's management. This study was conducted according to the Declaration of Helsinki and was approved by National Ethics Committee (Approval Nr. 37/07/09). All patients have received verbal and written information before written informed consent was obtained.

Biomarkers and echocardiography

Levels of biomarkers - ultrasensitive troponin T (usTnT) and N-terminal pro-B type natriuretic peptide (NT-proBNP) - were assessed at each visit. Whole blood samples were drawn by venepuncture and analysed using Roche's Elecsys® diagnostic analysis (Basel, Switzerland). A standard echocardiographic examination was performed by two experienced physicians (ML and RM). Cardiac chambers, valve abnormalities, systolic and diastolic function were evaluated. Left ventricular (LV) end-diastolic and end-systolic volumes were calculated using the Teicholtz or Simpson's biplane method.[23] The Teicholtz formula and Simpson's biplane method were used in patients with a struc-

turally normal LV and a structurally abnormal LV or diminished systolic function, respectively. Systolic function was evaluated by calculating left ventricular ejection fraction (LVEF) from LV end-diastolic and end-systolic volumes. Diastolic function was assessed using measurements of flow velocity at the opening of the mitral valve, septal tissue Doppler of the mitral annulus and volume of the left atrium. The ratio between E wave velocity at the mitral valve (E) and septal velocity of the mitral annulus (e′) was calculated (E/e′).[24]

Cut points and endpoint definitions

Elevated usTnT and NT-proBNP levels at visits 2 and 3 were defined as a > 30% increase from the visit 1 value. LVEF reduction was defined as a ≥ 10% or ≥ 5% decrease of LVEF to value ≤ 55% in asymptomatic and symptomatic patients, respectively, as suggested in trastuzumab trials.[25] Diastolic dysfunction was defined as E/e′ ≥ 15 or E/e′ < 15 and ≥ 8 with an enlarged left atrium, as recommended by the European Society of Cardiology.[24] Cardiotoxicity for an individual patient was defined as having increased usTnT or NT-proBNP or decreased LVEF at either visit 2 or 3.

Primary endpoint was cardiotoxicity, secondary endpoints were symptomatic heart failure, increased usTnT, NT-proBNP, LVEF reduction and diastolic dysfunction at visit 2 and 3, as described above.

Statistical analysis

Statistical analysis was performed using R 3.0.2 (R Development Core Team, Vienna, Austria) and the R package CVST (Krueger and Braun). Results are presented as the mean ± standard deviation for numeric variables and number (%) for nominal variables, except for the chemotherapy cycles, which are presented as median value and range. The paired t-test and Cochran's Q test were used to assess the changes at visit 2 and 3 from those at visit 1 for numeric variables and for binary variables, respectively. In univariate logistic regression models, we included cardiotoxicity as the dependent variable and sex, age, history of ischemic heart disease, history of arterial hypertension, metastatic lung cancer, number of chemotherapy cycles and usTnT, NT-proBNP and LVEF values at visit 1 as independent variables. In multivariate logistic regression models, we included cardiotoxicity as the dependent variable and history of ischemic heart disease, sex, age and LVEF at visit 1 as independent variables. For these analyses, results are presented as odds ratio (OR) with corresponding 95% confidence intervals (CI). A p value of less than 0.05 was considered to be statistically significant.

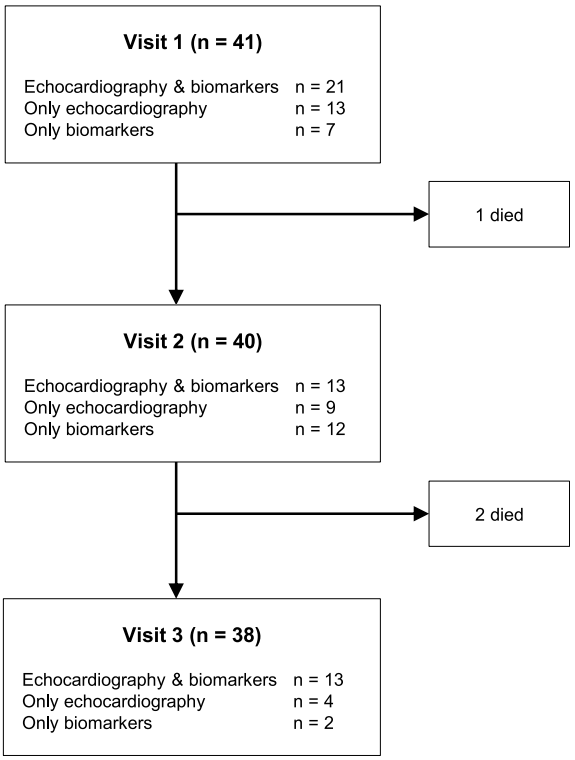

FIGURE 1. Study flowchart.

Results

Overall, 41 patients were included in the study between June 2012 and September 2013. 3 of the patients died during the study, all of them due to the cancer progression. At visit 2 and visit 3, 6 and 19 patients had an incomplete cardiac evaluation, respectively, mostly due to capacity related difficulties and patients' refusal at visit 2, and disease progression at visit 3. In all 3 visits, biomarkers were assessed in 7 patients, echocardiography was performed in 12 patients and both were assessed in 4 patients (Figure 1). All 40 patients who survived until visit 2 had information regarding primary endpoint.

Of 41 patients, 13 patients had early stage NSCLC and received adjuvant chemotherapy and 28 patients were given chemotherapy for metastatic disease (Table 2). In addition to cisplatin or carboplatin, all patients received one additional

TABLE 1. Patients' characteristics

Age – yr	61 ± 9
Male sex – no. (%)	22 (54)
Arterial hypertension – no. (%)	17 (41)
Ischemic heart disease – no. (%)	4 (10)
Cardiovascular disease – no. (%)	5 (12)
Glomerular filtration rate - ml/min/1.73 m^2	102 ± 28
Advanced disease – no. (%)	28 (68)

Where not mentioned, results are shown as mean values ± standard deviation. For calculating glomerular filtration rate, a modification of diet in renal disease study (MDRD) method was used.

TABLE 2. Chemotherapy treatment characteristics

Chemotherapy cycles – median (range)	4 (2-6)
Chemotherapy – no. (%)	
Cisplatin	28 (68)
Carboplatin	8 (20)
Both, in sequence	5 (12)
and	
Vinorelbine	11 (27)
Pemetrexed	22 (54)
Gemcitabine	8 (19)

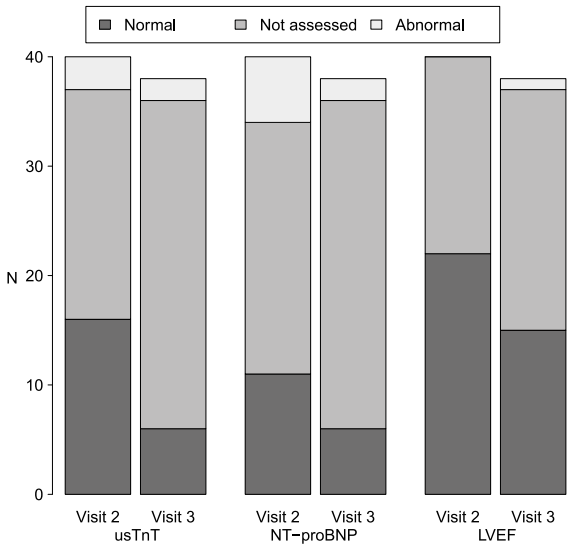

FIGURE 2. Number of patients at visit 2 or 3 with elevated usTnT, NT-proBNP and decreased LVEF form visit 1 values. Normal and abnormal was defined as > 30% increase in usTnT and NT-proBNP, and > 10% in symptomatic patients or > 5% in asymptomatic patients decrease to value lower than 50% in LVEF from visit 1 value.

LVEF = left ventricular ejection fraction; n = terminal pro BNP; NT = proBNP; usTnT = ultrasensitive troponin T

chemotherapeutic drug (vinorelbine, pemetrexed or gemcitabine).

At visit 1 or during the course of chemotherapy, none of the patients had overt symptoms or signs suggestive of heart failure or any other heart disease. CV disease was present in 5 patients (4 ischaemic heart disease and 1 peripheral artery disease). Of those with ischaemic heart disease 1 had older myocardial infarction while 3 had chronic ischaemic heart disease or angina pectoris. Differences in biomarkers and echocardiographic variables at each visit are shown in Table 3 and Figure 2. The values of usTnT and NT-proBNP gradually insignificantly decreased during the study, while the mean values of LVEF were not different between visits. ANOVA analysis included only patients with all measurements for each variable, therefore 7 and 12 patients were included in the analysis of biomarkers and LVEF, respectively. An increase of usTnT and NT-proBNP was observed in 4 and 7 patients at visit 2 or 3, respectively. None of the patients had decreased LVEF at visit 2, while 1 patient had decreased LVEF at visit 3. Patient who had decreased LVEF did not have increased values of NT-proBNP or usTnT, and one patient who had elevated NT-proBNP to more than 1800 pg/ml did not have decreased LVEF. While in some of the patients, the value of biomarkers increased, others experienced a decrease in values (Figure 3).

Primary endpoint was observed in 25% (10) out of 40 patients who survived until visit 2: 9 had increased values of biomarkers, and 1 had decreased LVEF. Univariate logistic regression models are shown in Table 4 where associations of different variables with corresponding ORs and 95% CI are given for each variable. Of all the variables tested in univariate logistic regression, history of ischemic heart disease was statistically significantly linked to cardiotoxicity (OR 12.86, 95% CI 1.16–142.88; p = 0.04). After adjusting for age, sex and LVEF value at visit 1, history of ischemic heart disease remained predictive of cardiotoxicity (OR 35.22, 95% CI 7.08–175.32, p = 0.023) (Table 5).

Discussion

Our results show that the treatment with platinum-based therapy did not induce clinically evident cardiotoxicity such as overt heart failure or other cardiac disease. Although no statistically significant or clinically important increase in the mean value for usTnT, NT-proBNP or decrease in LVEF or diastolic dysfunction was observed among the entire

TABLE 3. Biomarkers and echocardiography data

Variable	Visit 1	Visit 2	N	p-value	Visit 3	N	p-value
usTnT – pg/ml	11.4 ± 5.4	10.9 ± 5.1	19	0.93	8.3 ±3.2	8	1
>30% increase in usTnT from Visit 1 – no. (%)		3 (15.8)	19	1	2 (25)	8	1
NT-proBNP – pg/ml	266 ± 250	258 ± 378	17	0.55	226 ± 430	8	0.60
>30% increase in NT-proBNP from Visit 1 – no. (%)		6 (35.3)	17	1	2 (25)	8	1
LVEF - %	68 ± 8	67 ± 8	22	0.66	69 ± 9	16	0.63
>30% increase in LVEF from Visit 1 – no. (%)		0 (0)	22	1	1 (6)	16	1
Diastolic dysfunction – no. (%)	9 (27.3)	6 (27.3)	21	1	4 (23.5)	17	1

Results are shown as mean values ± standard deviation and differences were analysed with Paired t-test for numeric and Cochran's Q test for binomial variables.
LVEF = left ventricular ejection fraction; N = of patients with complete evaluation at visit 1 and 2 or visit 1 and 3, NT= proBNP, n-terminal pro BNP; usTnT = ultrasensitive troponin T

group, 25% of patients met the definition of cardiotoxicity. This phenomenon was largely driven by the known history of CV disease, even when adjusted to clinically relevant confounders.

Although platinum-based chemotherapy, as reported in animal models and case reports, could be associated with cardiotoxicity in patients with NSCLC, data from observational studies are lacking.[15-17] To our best knowledge, only one prospective study that investigated platinum-based cardiotoxicity in patients with NSCLC has been published.[22] The authors of that study measured LVEF with a multiple gated acquisition (MUGA) scan before and 3 months after treatment with cisplatin-gemcitabine (31 patients) or epirubicin-gemcitabine (38 patients). Study results showed a small and marginally significant decrease in the LVEF of 2% in the cisplatin-gemcitabine arm and a larger significant decrease in the LVEF of 7% in the epirubicin-gemcitabine arm. A larger decrease in the anthracycline arm was expected, which confirms that anthracycline chemotherapy is more cardiotoxic than platinum-based chemotherapy. Our results show a similar decrease in LVEF after platinum-based chemotherapy measured with echocardiography, which is less accurate for LVEF assessment but generally available, less expensive and can identify several other cardiac diseases compared to MUGA scanning. Due to similar results in both studies, echocardiography is possibly as efficient in detecting decreased LVEF as a sign of platinum-based cardiotoxicity as MUGA and represents a valid method that is more feasible for use in clinical practice.

Cisplatin and other platinum-based chemotherapy regimens are also used in other types of cancers, such as ovarian, testicular, prostatic and bladder. Some studies have measured cardiotoxicity of cisplatin in patients treated for testicular cancer.[18-20,26] Based on longer survival rates observed in patients with testicular cancer, there were several cohort studies that assessed long-term cardiotoxicity of more than 6 years.[19,20,26] The main findings of these studies were increased diastolic dysfunction and slightly decreased LVEF. Although the median age of patients diagnosed and treated for testicular cancer was approximately 35 years, several patients treated with cisplatin chemotherapy had cardiac events in the following years. Although the mean LVEF did not change after treatment, patients treated with cisplatin had a significantly higher risk for cardiovascular mortality and an increased rate of CV events compared to the general population. Similarly, in our study with a much shorter follow-up period, several patients experienced an important increase in biomarkers or

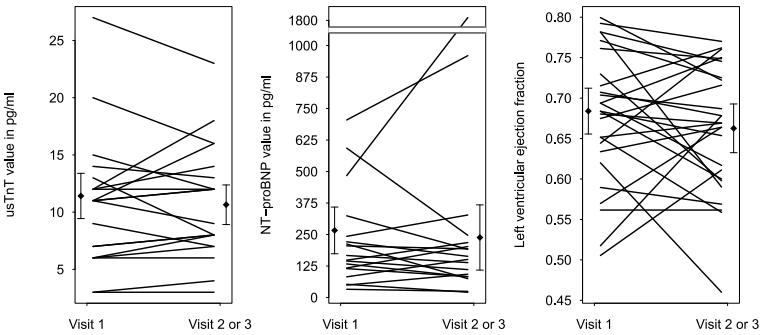

FIGURE 3. The mean with 95% CI and for each individual patient values of usTnT, NT-proBNP and LVEF at visit 1 and visit 2 or 3, whichever value was higher for usTnT and NT-proBNP and lower for LVEF.

CI = confidence interval; LVEF = left ventricular ejection fraction; n = terminal pro BNP; NT = proBNP; usTnT = ultrasensitive troponin T

TABLE 4. P values for univariate logistic regression models for cardiotoxicity

Independent variable	OR (95% CI)	p-value
Age in years	1.044 (0.955–1.142)	0.34
Male sex	0.824 (0.198–3.432)	0.79
Metastatic disease	0.765 (0.182–3.210)	0.71
History of ischemic heart disease	12.857 (1.157–142.880)	0.04
History of arterial hypertension	1.583 (0.377–6.649)	0.53
Glomerular filtration rate at Visit 1	1.000 (0.972–1.029)	1.00
No. of chemotherapy cycles	0.931 (0.474–1.827)	0.83
usTnT in pg/ml at Visit 1	0.961 (0.823–1.122)	0.62
NT-proBNP in pg/ml at Visit 1	1.000 (0.997–1.003)	0.93
LVEF in % at Visit 1	1.356 (0.000–37889.6)	0.95

LVEF = left ventricular ejection fraction; n = terminal pro BNP; NT = proBNP; usTnT = ultrasensitive troponin T

TABLE 5. Multivariate regression model for cardiotoxicity

Independent variable	OR (95% CI)	p-value
Age in years	1.044 (0.955 – 1.142)	0.52
Male sex	0.824 (0.198 – 3.432)	0.21
History of ischemic heart disease	12.857 (1.157 – 142.880)	0.026
LVEF in % at Visit 1	1.356 (0.000 – 37889.6)	0.92

OR = odds ratio; LVEF = left ventricular ejection fraction

decrease in LVEF. As none of these patients developed any symptoms or signs suggestive of heart failure or cardiac disease, the importance of this finding is uncertain. While elevations in troponin and BNP can indicate early preclinical cardiotoxicity, a decrease in LV systolic function measured by LVEF shows more extensive cardiac damage.[27] We can assume that patients who had elevations in biomarkers or lowered LVEF would have an increased risk for developing cardiac disease in the future.[28] For a minority of our patients with early lung cancer, a continuous cardiac surveillance is already planned. As we have evidence-based therapy for heart failure, screening (at least in high risk patients) should be part of routine clinical practice to detect or even prevent cardiac damage and possible cardiac events.

The findings of logistic regression model analysis suggest that patients who had a positive history of ischemic heart disease were more likely to have increased values of biomarkers or a decrease in LVEF after treatment and could be considered as those at risk and eligible for screening. Another group that would likely benefit from screening is the patients with a history of heart failure or left ventricular systolic dysfunction. With no such patients at visit 1, we were not able to test this hypothesis; given the risks and the availability of specific cardiac treatment[29,30], clinicians would hardly exclude these patients from a closer follow-up during chemotherapy.

We are aware of several limitations to this study. First, the sample size and several missing values for biomarkers and echocardiography could induce bias and limit the interpretation of the results. Patients were frequently assessed only using biomarkers or echocardiography, often only in visit 2 or visit 3, therefore complete assessment of both biomarkers and echocardiography is missing in several patients. Combining the elevated biomarker and decreased LVEF at either visit 2 or 3 allowed complete assessment of cardiotoxicity. Even though usTnT, NT-proBNP and LVEF are effected by different mechanisms, in asymptomatic patients, they are related to the development of preclinical cardiotoxicity. To further evaluate the extent of incomplete data a *post hoc* study power was calculated. For the same standard deviation and number of paired data as in our sample, we estimate that we had > 80% power to detect a > 3 pg/ml, > 250 pg/ml and > 7% increase/decrease in usTnT, NT-proBNP and LVEF, respectively. Second, blood for biomarkers was not taken immediately after the chemotherapy cycle but on day 1 of the following cycle. Therefore, any changes in biomarker values could not reflect the acute effect of the platinum-based chemotherapy cycles, as elevations in NT-proBNP and usTnT persist for 1-2 weeks, but the interval between platinum doublets used in our patients was 3 weeks.[31] Last, in our 6-month follow-up, we were unable to evaluate long term cardiotoxicity. Although patients with advanced stage NSCLC most likely would not develop long-term cardiotoxicity, patients with early stage NSCLC with longer survival could. To answer this question, future studies exploring LVEF and biomarker changes and possible development of overt heart failure in those with preclinical cardiotoxicity in early stage NSCLC patients treated with platinum-based chemotherapy are necessary.

Despite its limitations, we think that this study is important, because it is the second study to evaluate cardiotoxicity in NSCLC patients treated with platinum-based chemotherapy. We were able to detect changes in cardiac biomarkers and to identify patients who may be at risk for devel-

oping cardiotoxicity. Long-term platinum-based cardiotoxicity has already been observed in other cancers[19,20,26], and with the invention of new anticancer therapies leading to a longer life expectancy for patients with NSCLC, screening for early cardiac injury might become an important part of care for patients with NSCLC, particularly those with early disease. With other concomitant or sequential treatments, such as radiotherapy and targeted therapies, even small cardiotoxic effects of individual type of therapy could contribute to late cardiotoxicity and higher cardiac mortalities as shown in other types of cancers.[10] Detection of early cardiac injury may facilitate early therapeutic measures and healthy lifestyle modifications in patients with NSCLC who have a good prognosis, thus leading to better survival rates in those patients.

Conclusions and clinical implications

Our study shows that platinum-based therapy in patients with NSCLC did not induce clinically overt acute or subacute cardiotoxicity. Despite the fact that mean values of biomarkers and LVEF did not change significantly after treatment, 25% of patients experienced changes defined as cardiotoxic. We have shown that patients with a history of ischemic heart disease were more likely to experience an increase in laboratory biomarkers or a decrease in LVEF. Therefore, we suggest assessing LVEF and laboratory biomarkers to screen for cardiotoxicity in patients with NSCLC treated with platinum-based chemotherapy who have a history of ischemic heart disease, heart failure or asymptomatic left ventricular dysfunction. Further research should focus on patients with a history of cardiac disease, patients with longer life expectancy - especially in early stage NSCLC - and any novel biomarkers that may emerge in the future.

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