Cardiotoxicity in Advanced Non-small Cell Lung Cancer Patients Treated with Platinum and Non-platinum Based Combinations as First-line Treatment

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Abstract. Background: One of the major dose-limiting toxicities of anthracyclines is cardiotoxicity due to irreversible cardiomyopathy. Whether cisplatin-based treatment induces cardiotoxicity in the short term, especially in non-small cell lung cancer (NSCLC) patients with cardiovascular comorbidity, has not been studied previously. The aim of this study was to evaluate cardiotoxicity in advanced NSCLC patients receiving cisplatin-gemcitabine (CG) or epirubicin-gemcitabine (EG) as first-line treatment. Patients and Methods: Patients were randomised to receive gemcitabine 1125 mg/m² (days 1 and 8) plus either cisplatin 80 mg/m² (day 2) or epirubicin 100 mg/m² (day 1) every 3 weeks for a maximum of 5 cycles. Patients had to have a left ventricular ejection fraction (LVEF) > 45%, measured by multiple gated acquisition (MUGA) scan. A second MUGA scan was performed 12 weeks after the end of treatment. Results: Sixty-nine patients were included. The mean total dose of cisplatin was 349 mg/m² and of epirubicin 452 mg/m². The mean difference in decline in LVEF from baseline was 2% in the CG arm versus 6% in the EG arm (p=0.016). Clinically evident cardiac failure was not observed during 12 months follow-up. No correlation was found with total drug doses administered. In patients with a history of cardiac disease a trend towards a higher decrease in LVEF was observed. Conclusion: Although in the EG arm the LVEF significantly declined and in the CG arm a trend for LVEF to decline was observed, the risk of cardiac failure is limited in advanced NSCLC patients.

Platinum-based chemotherapy is standard treatment for patients with advanced non-small cell lung cancer (NSCLC) who have a good performance status (1). Treatment regimens of cisplatin or carboplatin in combination with newer agents such as paclitaxel, docetaxel, gemcitabine and vinorelbine prolong survival and improve quality of life compared to older platinum-based regimens in advanced NSCLC (2). Recently, also a small survival advantage of adjuvant cisplatin-based chemotherapy was shown in NSCLC patients with operable disease (3). However, two older large randomised trials did not demonstrate an improved survival in this group of patients (4, 5). Whether induction cisplatin-based chemotherapy is beneficial in early stage NSCLC is the subject of ongoing trials. Due to these potentially new indications, an increasing number of patients with early stage NSCLC, who can expect a longer overall survival compared to patients with advanced disease, will be treated with cisplatin-based chemotherapy.

However, cisplatin has several disadvantages such as nephro-, neuro- and ototoxicity. Long-term follow-up studies in metastatic testicular cancer patients cured by cisplatin-based chemotherapy also showed an unfavourable cardiovascular risk profile (6, 7). Whether cisplatin induces subclinical myocardial toxicity in the short term and in an older age group, has not been studied previously. Since a high percentage of patients with NSCLC has cardiovascular comorbidity (8), we were especially interested in potential cisplatin-induced cardiotoxicity.

Non-platinum-containing regimens have been studied to find less toxic therapies, which preferably do not require hospitalisation. Epirubicin-based treatment is one possible alternative. Epirubicin, the 4’ epimer of the anthraclyline antibiotic doxorubicin, has demonstrated antitumour activity in NSCLC. The major acute dose-limiting toxicity of anthracyclines is myelosuppression. Cardiotoxicity, manifested as irreversible congestive heart failure and/or...
cardiomyopathy, is the most important chronic cumulative doSELimiting toxicity. Cardiotoxicity increases sharply with higher cumulative epirubicin doses.

The most frequently reported toxicity in phase II trials with high-dose epirubicin in advanced NSCLC was myelosuppression, followed by mucositis (9-11). The 79 patients included in these three trials received doses between 135-150 mg/m^2 every 3 weeks. At cumulative doses between 435-950 mg/m^2, 7 patients (8.9%) had a drop of ≥ 15% in left ventricular ejection fraction (LVEF) compared to baseline values. No signs of congestive heart failure were found.

Two-drug combination regimens of epirubicin and other agents such as etoposide, vinorelbine, cisplatin and paclitaxel were investigated as first-line regimens in NSCLC. In 5 trials a total of 227 patients were treated with epirubicin-containing combination regimens with a maximum cumulative epirubicin dose of 540-840 mg/m^2 (12-15). In these trials LVEF was evaluated by MUGA scan in 77 patients. A total of 12 patients (15.6%) had a drop of more then 15% in LVEF. No signs of congestive heart failure were found, but cardiac arrhythmias were observed in 5 patients.

In our institution the activity of epirubicin combined with gemcitabine in advanced NSCLC was studied in a phase I and II study where the maximum cumulative dose of epirubicin was 500 mg/m^2 (16). Haematological toxicity was granulocytopenia grade 4 in 33% and thrombocytopenia grade 4 in 12% of the cycles. Feverle neutropenia occurred in 14% of the patients. Nonhaematological toxicity was mainly mucositis grade 2 and 3 in 35% of the patients. The median decrease in LVEF measured by multiple gated acquisition (MUGA) scan was 7.2%. Patients did not show clinical signs of heart failure during follow-up.

Radionuclide ventriculography or MUGA scan has been widely applied as a standard non-invasive method in identifying subclinical anthracycline cardiotoxicity in adult patients (17). Nousiainen et al. found that a decrease in LVEF of more than 4% units from baseline after a cumulative doxorubicin dose of 200 mg/m^2 had a 90% sensitivity and 72% specificity for predicting later cardiotoxicity in lymphoma patients (18). However, others report a lower sensitivity (53%) and a specificity of 75% compared to abnormalities found in myocardial biopsy specimens (19).

We evaluated myocardial functioning with MUGA scan in 69 NSCLC patients treated with cisplatin and gemcitabine (CG) or epirubicin and gemcitabine (EG) before and after chemotherapy.

Patients and Methods

Patient selection and treatment. Patients were included if they had histological or cytological diagnosis of unresectable stage III or IV NSCLC. No prior chemotherapy or radiotherapy in the chest region was allowed. All patients had to have a performance status ≤ 2 according to the Eastern Cooperative Oncology Group (ECOG) scale, a life expectancy of at least 12 weeks and a LVEF > 45%, as measured by MUGA scan. Patients with recent myocardial infarction were excluded.

Eligible patients were randomised to receive either cisplatin or epirubicin both with gemcitabine (1125 mg/m^2) administered during a 30-minute infusion on days 1 (before cisplatin or epirubicin) and 8. Cisplatin 80 mg/m^2 was administered intravenously over 3 hours after prehydration with 0.9% NaCl on day 2 of each 21-day treatment cycle. Epirubicin 100 mg/m^2 was administered intravenously over 3 hours after prehydration with 0.9% NaCl on day 2 of each 21-day treatment cycle. Treatment consisted of a maximum of 5 cycles and was discontinued earlier in case of tumour progression, intolerable toxicity or patient’s wish. The mean relative dose-intensity was calculated by dividing the delivered dose (mg/m^2/week) by the planned dose (mg/m^2/week) for the number of cycles each patient received.

The local medical ethics committee approved the protocol. All patients gave informed consent before study entry.

Cardiotoxicity evaluation. The LVEF at rest (normal range 55 - 65%) was measured by MUGA scan immediately before and about 12 weeks after the end of treatment. A LVEF < 50% was classified as abnormal. A MUGA scan was performed after in vivo labelling of red blood cells. For this labelling an injection of stannous chloride was followed by 500 MBq technetium-99m pertechnetate about 20 minutes later. A 3-lead ECG was connected to the patient. Acquisition was performed with a Siemens Diacam single-head gamma camera (Siemens, Forchheim, Germany) with a low energy all-purpose parallel-hole collimator. Measurements were taken in the left anterior oblique 30-degree projection during 6 minutes with 20 frames per cardiac cycle.

During follow-up evaluation included toxicity scoring according to the Common Toxicity Criteria (CTC) of the National Cancer Institute, with special reference to cardiotoxicity, every 6 weeks.
chest X-ray was performed every 6 weeks to assess tumour progression. The follow-up period was at least one year after discontinuation of treatment, unless the patient died earlier.

Symptoms related to cardiotoxicity, such as fatigue and dyspnea, were evaluated at the start of treatment, after 3 cycles of chemotherapy and 6 weeks after the end of treatment with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, supplemented by a 13-item lung cancer-specific module, the EORTC QLQ-LC13 (20, 21).

Statistical analysis. The Student’s t-test was used to analyse the difference between LVEF before and after treatment. Normality of distributions was assessed using the Kolmogorov-Smirnov test. Differences between both arms in decrease in LVEF according to CTC-criteria were compared by Chi-square test. Spearman’s correlation coefficient was used to evaluate the relationship between the total drug doses administered and decrease in LVEF. Pearson’s correlation coefficient was calculated for correlation of a decrease in LVEF and age. To identify potential prognostic factors, a multivariate analysis was performed using a logistic regression model for decrease in LVEF. Quality of life was analysed by ANOVA for the different functional areas and symptoms at all three points of measurement. A $p<0.05$ was considered statistically significant.

Results

Patient characteristics. In this cardiotoxicity analysis 69 patients, who were enrolled in a randomised phase III trial (22) and had a second MUGA scan after treatment, were analysed. Thirty-one patients were treated with CG and 38 patients with EG. The second MUGA scan was performed about 12 weeks after treatment. None of the other patients included in the phase III trial had clinically evident cardiotoxicity at 12 weeks posttreatment evaluation.

The patient characteristics were not significantly different between both treatment arms (Table I). One patient in the EG arm had malignant pericardial effusion. In both arms, four patients had a history of cardiac disease: myocardial infarction more than one year before treatment (2 in CG arm, 3 in EG arm), mitral valve regurgitation after myocardial infarction (1 in CG arm), aortic stenosis (1 in CG arm), aortic stenosis and myocardial infarction (1 in EG arm).

Drug exposure. The mean ($\pm$ SE) total doses of cisplatin ($n=31$) and epirubicin ($n=38$) were $349\pm13\ mg/m^2$ and $452\pm10\ mg/m^2$, respectively. The total dose (mean$\pm$SE) of gemcitabine was $9648\pm361\ mg/m^2$ in the CG arm and $9943\pm243\ mg/m^2$ in the EG arm ($p>0.05$). The mean relative dose-intensity for cisplatin and epirubicin was 96% and 95%, respectively. The mean relative dose-intensity of gemcitabine was not significantly different between both treatment arms; 94% for the CG arm and 92% for the EG arm.

The mean ($\pm$ SE) number of cycles administered was $4.4\pm0.2$ versus $4.6\pm0.1$ in, respectively, the CG and EG arm. The maximum of 5 cycles was completed in 18 (58%) patients in the CG arm and in 26 (68%) patients in the EG arm. Patients in the CG arm more frequently requested discontinuation of treatment ($p<0.05$). However, treatment discontinuation due to toxicity was not different in both arms (Table II).

Cardiotoxicity. Baseline values of the LVEF were similar in both arms ($p=0.254$). The LVEF declined significantly in the EG arm but showed only a trend to decrease in the CG arm (Table III). The mean difference in decline in LVEF from baseline was 2% in the CG arm versus 6% in the EG arm ($p=0.016$). Before treatment six patients in the CG arm and three patients in the EG arm had a LVEF below 50%. After treatment seven patients in the CG arm and twelve patients in the EG arm had a LVEF below 50%. An absolute drop of more then 15% in LVEF was observed in one patient in the CG arm (3%) versus three patients in the EG arm (8%).

According to CTC criteria a grade 1 (decline in LVEF $\geq 10\%$ but < $20\%$ of baseline value) and grade 2 (decline in LVEF $\geq 20\%$ of baseline value) decline in LVEF occurred in, respectively, 16% and 7% of patients in the CG arm versus in 42% and 13% of patients in the EG arm ($p=0.006$, for differences between both arms). No CTC grade 3 or 4 decline in LVEF occurred.

Median ($\pm$ SE) follow-up was $53.4\pm4.9$ weeks. Clinically evident signs of congestive heart failure were not observed.
in either arm during follow-up. No symptoms of fatigue or dyspnea due to cardiac causes were reported. One patient experienced a non-Q wave myocardial infarction during treatment with EG. This patient was surgically treated for abdominal aortic aneurysm one year before lung cancer was diagnosed, but had no history of cardiac disease. The LVEF of this patient decreased from 57% to 34% after treatment. Another patient had malignant pericardial effusion, while the LVEF before and after EG treatment remained stable (48%). One patient, with a LVEF of 54% after CG treatment, developed paroxysmal atrial fibrillation 12 months after discontinuation of this therapy. Four weeks later this patient died due to progression of liver metastases. Before treatment LVEF was not significantly lower in patients with a history of myocardial infarction, aortic stenosis or mitral valve regurgitation compared to other patients, respectively 55±3% and 58±1% (p=0.265). After treatment LVEF was 48±3% in patients with a history of cardiac disease and 54±1% in other patients (p=0.057).

No correlation was found between decrease in LVEF and the total administered doses of either cisplatin, epirubicin or gemcitabine. Likewise, no correlation was found between the total number of cycles administered and decrease in LVEF. A decrease in LVEF was positively correlated with age (Pearson’s correlation coefficient=0.27, p<0.05).

A logistic regression model was used to identify potential prognostic factors for a CTC grade 1 or 2 decrease in LVEF. We used gender, age, performance status, baseline LVEF and history of cardiac disease (myocardial infarction or valve dysfunction) as covariates. None of these covariates in this model was identified as a significant independent predictor.

Chest X-rays showed no signs of cardiac failure. A chest X-ray is not capable of detecting early signs of anthracycline-induced cardiotoxicity, but in a late stage when signs of congestive heart failure are present, cardiomegaly or pulmonary edema can be detected (23).

The quality of life questionnaires at the start of treatment, after 3 cycles of chemotherapy and 6 weeks after the end of treatment were returned by 87%, 67% and 71% of patients, respectively. At all three times of measurement, no significant differences in symptom scales related to cardiotoxicity (fatigue and dyspnea) were found between either treatment arm.

**Discussion**

Cisplatin in combination with gemcitabine for the treatment of NSCLC showed only a trend to decline in LVEF. In this trial the mean decrease in LVEF was 2% in the CG arm versus 6% in the EG arm. In patients with a history of myocardial infarction, aortic stenosis or mitral valve regurgitation, a trend towards a higher decrease in LVEF was observed. We found a weak correlation between age and decrease in LVEF.

Due to the poor survival of patients with stage III and IV NSCLC, follow-up in most patients was slightly over one year. During this follow-up period no signs of congestive heart failure were observed. However, epirubicin can induce a slowly progressive deterioration of cardiac function continuing years after treatment (24), which was probably not observed in this trial because of the poor survival. Gemcitabine probably scarcely adds to cardiotoxicity in doublet treatments. Gemcitabine added to cisplatin only showed a trend to a subclinical decline in LVEF. In contrast, cisplatin administered in doses such as in this study might be cardiotoxic, especially in long-term survivors of metastatic testicular cancer who develop an unfavourable cardiovascular risk status and cardiovascular events (7). Whether cisplatin-based treatment induces clinically relevant cardiotoxicity in long-term survivors of early stage NSCLC is currently unknown.

The risk of anthracycline-related cardiomyopathy correlates strongly with cumulative dose. In patients with advanced breast cancer, Jensen et al. (24) found a 25% relative reduction in LVEF in 15% of patients 3 weeks after treatment discontinuation, increasing to 59% of patients 3 years after treatment, at a cumulative dose of 850-1000 mg/m² epirubicin. One year after terminating epirubicin therapy, 11% of the patients deteriorated to a severely dilated congestive heart failure, increasing to 20% after 5 years (24). Ryberg et al. found an exponentially increasing cumulative risk of congestive heart failure from 4% at 900 mg/m² epirubicin to 15% at 1000 mg/m² in breast cancer patients (25). In accordance with our results, in other studies a decrease in LVEF of 3-7% was found in breast cancer patients treated with epirubicin at cumulative doses below 500 mg/m² at one year follow-up (26, 27). Pre-existing cardiac disease and advanced age as other risk factors for anthracycline cardiotoxicity were also found by others (24, 28). Previous thoracic radiotherapy is an additional proposed risk factor for cardiac damage (29). However, in our trial no patients had been pre-treated with thoracic radiotherapy.

Although in the CG arm a trend to decline in LVEF was observed and a significant decline in LVEF was observed in the EG arm, the risk of chemotherapy-induced cardiac death is presumably very low in patients with advanced NSCLC. Since in the future probably more patients with early stage NSCLC will be treated with cisplatin-based chemotherapy, cardiotoxicity should be evaluated during long-term follow-up in other trials, with special focus on patients with a history of cardiac disease. Plasma troponin levels correlate with anthracycline-induced cardiotoxicity (30). Whether plasma troponin level evaluation is useful for follow-up of patients treated with cisplatin is currently unknown.

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References


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