Impact and Safety of Adjuvant Chemotherapy on Pulmonary Function in Early Stage Non-Small Cell Lung Cancer

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Key Words

Adjuvant chemotherapy · Pulmonary function · Non-small cell lung cancer · Toxicity

Abstract

Background: Pulmonary function may decline after induction chemotherapy and predict perioperative complications in non-small cell lung cancer (NSCLC). The influence of adjuvant chemotherapy is largely indeterminate. **Objective:** To assess whether adjuvant chemotherapy alters pulmonary function and impacts on treatment-related adverse events. **Methods:** In a trial on adjuvant chemotherapy (the TREAT trial), 132 patients with R0-resected NSCLC were randomised to 4 cycles of cisplatin-vinorelbine (CVb, n = 65) or cisplatin-pemetrexed (CPx, n = 67). Pulmonary function tests (forced expiratory volume in 1 s, FEV₁, forced vital capacity, FVC, total lung capacity, TLC, diffusing capacity for carbon monoxide, DLCO, and blood gas analyses, BGA) were analysed before

and 30 days after the last chemotherapy, and changes were calculated (Δ = mean differences). **Results:** Overall, FVC increased significantly (Δ +290 ml, n = 76; p < 0.0001), while TLC did not change (Δ +220 ml, n = 41; p = 0.174). For CPx, FEV₁ increased significantly (Δ +150 ml, n = 47; p = 0.0017), but not for CVb (Δ +30 ml, n = 30). DLCO decreased only for CVb (–8%, n = 6) but not for CPx (–0.39%, n = 17; p = 0.58). BGA did not change (p = 0.99). In a Cox regression analysis, baseline pulmonary function did not influence treatment failure. **Conclusions:** Adjuvant chemotherapy seems not to result in a decrease of pulmonary function parameters. A significant FVC increase was probably due to ongoing postoperative improvement. Decline of DLCO was noted with CVb but not with CPx. Pulmonary function does not impact on treatment failure.

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A list of TREAT collaborators can be found in the Appendix.

Introduction

In a considerable subset of lung cancer patients, pulmonary function is impaired, mainly due to a significant association of chronic obstructive pulmonary disease (COPD) and lung cancer [1]. Several factors have been reported to influence pulmonary function in non-small cell lung cancer (NSCLC) patients, including radio- and chemotherapy. Radiation pneumonitis may occur in 5–15% of patients [2] and significant loss of pulmonary function has been reported for certain chemotherapeutic drugs in the treatment of NSCLC, mainly gemcitabine and taxanes [3–6]. In patients with resectable lung cancer, assessment of standard pulmonary function tests is crucial to decide on curative intent surgery. These also guide further functional tests or even exclude patients from surgery [7].

Recent trials have shown that adjuvant cisplatin-based chemotherapy in patients with early stage NSCLC significantly increases overall survival [8]. However, several issues in the adjuvant treatment still need to be addressed, e.g. the impact of age and comorbidities, the best combination partner for cisplatin in regard to efficacy and feasibility, the acute toxic effects and the influence on patient quality of life [9].

As the lung is a potential target of drug and especially chemotherapy toxicity, the effect of adjuvant chemotherapy on pulmonary function needs further attention. While several trials have focused on the toxic effects of neoadjuvant chemotherapy on pulmonary function or the course of lung function after major lung resection without neo-/adjuvant therapy [5, 10–12], no data exist on the impact of adjuvant chemotherapy on pulmonary function in early-stage NSCLC. The most common chemotherapy regimen in adjuvant clinical trials was cisplatin-vinorelbine (CVb) [13]. For vinorelbine, a semi-synthetic vinca alkaloid, acute and subacute toxic pulmonary side effects have been reported, associated with acute dyspnoea, bronchospasm, alveolar infiltrates, diffuse interstitial infiltrates and, in rare cases, acute respiratory distress syndrome [14, 15]. For platinum compounds, mainly oxaliplatin, the pulmonary side effects include interstitial lung disease, mainly cryptogenic organizing or eosinophilic pneumonia, and diffuse alveolar damage [16–18]. However, an association between pulmonary function decline and cisplatin or vinorelbine has not been reported yet. For pemetrexed, which was administered in combination with cisplatin in our recently reported adjuvant phase II trial comparing this doublet to CVb [19], significant pulmonary toxicity has

not been reported in phase III studies on advanced NSCLC [20, 21], although there is casuistic evidence [22].

The aim of this analysis was to assess whether adjuvant chemotherapy either with cisplatin-pemetrexed (CPx) or CVb alters pulmonary function and impacts on treatment-related adverse events in the context of a phase II randomised trial on adjuvant chemotherapy in early-stage NSCLC [19, 23].

Materials and Methods

Patients and Treatment

Patients who were treated within the TREAT trial (Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy; ClinicalTrials.gov identifier NCT00349089) were included in this analysis [19, 23]. They were randomly assigned to either CPx or CVb adjuvant chemotherapy. The study was approved by the institutional review board of each participating institution, and all patients provided informed consent. The ethics committee of the University of Heidelberg served as a central ethics committee (approval number AF-mu-115/2006). The trial design, treatment plan, endpoints, eligibility criteria, toxicity management and follow-up modalities, as well as its results on the primary endpoint, were previously reported in detail [19]. Briefly, patients who had fully recovered after complete tumour resection with pathologically confirmed NSCLC stages IB, IIA, IIB or T3N1 (according to the TNM staging system version 6 [24]) and without need for further radiotherapy were included. Within 4–6 weeks postoperatively, patients were randomly assigned to 4 cycles of chemotherapy. The experimental arm consisted of cisplatin (75 mg/m², day 1) plus pemetrexed (500 mg/m², day 1) with vitamin-supplementation (folic acid and vitamin B₁₂) and dexamethasone (4 mg of oral or equivalent, given twice daily the day before, the day of and the day after each dose of pemetrexed for rash prophylaxis, unless medically contraindicated). The comparator consisted of cisplatin (50 mg/m², day 1, 8) plus vinorelbine (25 mg/m², days 1, 8, 15, 22) every 4 weeks [25]. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria and was classified by grade, type, duration, onset and relationship to study treatment according to CTCAE version 3.0 [26].

Pulmonary Function Tests

Baseline pulmonary function assessments with pulmonary function tests (PFTs), capillary blood gas analysis (BGA) and diffusing capacity for carbon monoxide (DLCO) were performed within 14 days prior to initiation of chemotherapy according to the current ATS/ERS recommendations. Follow-up PFTs, BGA and DLCO were assessed 30 days after the last cycle of chemotherapy (fig. 1). PFTs consisted of spirometry to determine forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁), and lung volumes were measured using body-box plethysmography to measure total lung capacity (TLC). Furthermore, DLCO using the single-breath breath-holding technique was assessed. BGA measurements evaluated arterial partial pressures of oxygen (PaO₂), carbon dioxide (PaCO₂) and oxygen saturation (SaO₂). Results for FVC, FEV₁, TLC, and DLCO are reported as absolute values, while the

Fig. 1. CONSORT diagram of the PFT analyses of the TREAT study. R0 = Complete resection.

FEV₁/FVC ratio is reported as an absolute percentage. Mean changes of pulmonary function parameters were calculated and analysed per treatment arm as well as for the total group (Δ = mean differences; n = numbers reported).

Statistical Analysis

All parameters were evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. All p values were two sided if not otherwise stated. Pulmonary function and toxicity were calculated, providing confidence intervals. Comparisons between patient groups were analysed by t test. The event-related time to treatment failure was estimated by the Kaplan-Meier product limit method and compared using the log-rank test. Time to treatment failure was defined as the time from surgery to the time the patient was withdrawn due to adverse events, tumour relapse, death, failure to return, refusal of treatment or consent withdrawal [19, 23]. Multivariate analyses were performed by Cox regression analysis. Changes in PFT values were analysed using the Wilcoxon signed-rank test, with $p < 0.05$ considered to be statistically significant.

Results

Patient Characteristics

From October 2006 to December 2009, 132 patients at 16 sites were randomly assigned to CPx (n = 67 patients) or CVb (n = 65 patients). The patients' baseline characteristics are shown in table 1. The median age of all patients was 59 years. 95% of the patients were current or ex-smokers with a median of 40 pack years. Mean FVC was 2.92 litres, mean FEV₁ was 2.01 litres, mean FEV₁/FVC was 70.4% and mean DLCO was 58.5% prior to adjuvant chemotherapy. Fifty-four out of 132 patients (41%) were diagnosed with COPD, 30 in the CPx and 24 in the CVb arm. Of these, according to the GOLD 2001 classification [27], 43% had COPD grade I, 24% had grade II, 4% had grade III and 29% were not graded. Besides 2 patients with controlled asthma (1 patient per treatment arm), there were no further pulmonary comorbidities.

Table 1. Patient characteristics

	CPx (n = 67)	CVb (n = 65)	Total (n = 132)
Age, years	58	60	59
Range	40–73	38–74	38–74
Gender, %			
Male	72	77	74
Female	28	23	26
Smoking status, %			
Smoker	33	26	29
Ex-smoker	61	71	66
Non-smoker	6	1.5	4
Not available	0	1.5	1
Surgical procedures, %			
Lobectomy	84	82	83
Pneumonectomy	12	15	14
Complex resections	4	3	3
Baseline PFT and BGA			
FEV ₁ , litres	1.97±0.53	2.07±0.62	2.01±0.57
TLC, litres	5.6±1.65	5.33±1.59	5.48±1.62
FVC, litres	2.91±0.83	2.94±0.68	2.92±0.76
DLCO, %	58.5±24.7	58.67±21.7	58.5±23.4
FEV ₁ /FVC, %	71.2±14.3	69.6±12.2	70.4±13.3
SaO ₂ , %	95.6±1.9	95.8±1.9	95.7±1.9
PaO ₂ , mm Hg	75.1±7.4	77.3±8.7	76.2±8.1
PaCO ₂ , mm Hg	36.6±4.5	38.1±8.1	37.4±6.6
Diagnosis of COPD ¹ , n			
I	13	10	23
II	9	4	13
III	1	1	2
Not graded	7	9	16
Under therapy with bronchodilators	17	11	28

Values are numbers or percentages, as indicated, or means ± standard deviation.

¹ Spirometric classification of COPD according to GOLD 2007.

Chemotherapy delivery was 90% of the planned dose in the CPx arm, while in the CVb arm this was 66% for cisplatin and 64% for vinorelbine, respectively. The two groups were evenly distributed with respect to age, gender, smoking status, performance status, stage, surgical procedures, histologic features and baseline lung function parameters, including DLCO and BGA.

Therapy-associated pulmonary toxicities were mild and grade 3/4 toxicity did not occur in either arm. The most frequent pulmonary toxicities were grade 1/2 cough (CPx 13.4%, CVb 7.7%) and dyspnoea (CPx 9%, CVb 4.6%). Pneumonia was noted in 1 patient in the CPx arm, and bronchitis was reported in 1 patient in each arm. COPD exacerbations were not reported.

Table 2. Mean changes in PFT and BGA before and 30 days after chemotherapy

Parameter	CPx	CVb	Overall population
ΔFVC, ml	+320	+260	+290
Range	–430 to +940	–1,680 to +1,150	–1,680 to +1,150
Patients, n	46	30	76
ΔFEV ₁ , ml	+150	+30	+100
Range	–910 to +1,220	–2,870 to +580	–2,870 to +1,220
Patients, n	47	30	77
ΔTLC, ml	+150	+380	+220
Range	–4,080 to +2,850	–1,060 to 1,770	–4,080 to +2,850
Patients, n	28	13	41
ΔDLCO, %	–0.39	–8	–2.4
Range	–41 to +77	–44 to +50	–44 to +77
Patients, n	17	6	23
ΔFEV ₁ /FVC, %	–2.3	–1.66	–2.0
Range	–16 to +21	–13 to +10	–16 to +21
Patients, n	45	29	74
ΔPaO ₂ , mm Hg	+0.63	–0.80	–0
Range	–19 to +21	–13 to +15	–19 to +21
Patients, n	32	25	57
ΔSaO ₂ , %	–0.26	+0.32	0
Range	–3.8 to +2.5	–3.4 to +4	–3.8 to +4
Patients, n	30	24	54
ΔPaCO ₂ , mm Hg	+0.85	–3	–0.73
Range	–5 to +12	–58 to +6	–58 to +12
Patients, n	32	26	58

Pulmonary Function Changes after Chemotherapy

Mean changes of pulmonary function parameters analysed per treatment arm as well as for the total group are reported in table 2. In the total patient group, FVC (Δ +290 ml, n = 76; p < 0.0001) and FEV₁/FVC (Δ –2.0%, n = 74; p = 0.00097) changed significantly, while TLC (Δ +220 ml, n = 41; p = 0.174), FEV₁ (Δ +100 ml, n = 77; p = 0.054) and DLCO (Δ –2.4%, n = 23; p = 0.687) did not change significantly.

In the CPx group, FEV₁ (Δ +150 ml, n = 47; p = 0.0017), FVC (Δ +320 ml, n = 46; p < 0.0001) and FEV₁/FVC (Δ –2.3%, n = 45; p = 0.029) changed significantly, while TLC (Δ +150 ml, n = 28; p = 0.506) and DLCO (Δ –0.39%, n = 17; p = 0.953) did not change significantly. In the CVb group, FVC (Δ +260 ml, n = 30; p = 0.006) increased significantly, while FEV₁ (Δ +30 ml, n = 30; p = 0.788), FEV₁/FVC (Δ –1.66%, n = 29; p = 0.174), TLC (Δ +380, n = 13; p = 0.069) and DLCO (Δ –8%, n = 6; p = 0.5824) did not change significantly. Of note, DLCO decreased only for CVb (–8%, n = 6) but not for CPx (–0.39%, n = 17; p = 0.58; fig. 2) and FEV₁ increased significantly only for CPx (Δ +150 ml, n = 47; p = 0.0017), and not for CVb (Δ +30 ml, n = 30).

Fig. 2. Change of DLCO before (baseline) and 30 days after therapy (end of therapy) for CPx (n = 17) compared to CVb (n = 6; p = 0.58).

For BGA, significant changes for PaO_2 , PaCO_2 or SaO_2 were not found in the overall group (PaO_2 , Δ 0 mm Hg, n = 57; p = 0.999; SaO_2 , Δ 0%, n = 54; p = 0.987; PaCO_2 , Δ -0.73 mm Hg, n = 58; p = 0.501) or in the subgroups (data not shown). In the multivariate Cox regression analysis, changes of pulmonary function parameters including DLCO and BGA did not affect adverse events, death, treatment refusal or non-compliance to chemotherapy (FEV_1 , p = 0.503; FVC, p = 0.804; TLC, p = 0.815; PaO_2 , p = 0.655; PaCO_2 , p = 0.741; DLCO, p = 0.520).

Discussion

The present investigation is the first report on the safety and effects of adjuvant chemotherapy on pulmonary function in patients with early stage NSCLC. Lung surgery in NSCLC patients leads to a decrease in pulmonary function in a population with common concomitant lung disease, mainly COPD. Hence, these patients have a reduced ability to tolerate further loss in pulmonary function. Therefore, preoperative pulmonary assessment is mandatory in these patients [7]. An impairment of pulmonary function, which has been reported by several authors either pre- or postoperatively [5, 10–12, 28], might further endanger patients planned for curative intent surgery, especially patients with NSCLC receiving induction chemotherapy or chemoradiotherapy. However, the effects of adjuvant, i.e. postoperative, chemotherapy on pulmonary function are not well described. Theoretically, as significant impact on pulmonary function with some chemotherapeutic drugs in the treatment of NSCLC

has been reported [3–6], adjuvant chemotherapy might be an additional risk for postoperative and/or chemotherapy-related complications. Our data, however, do not support this hypothesis, as a detrimental effect of chemotherapy on pulmonary function was not found. In fact, pulmonary function did not affect adverse events and significant pulmonary toxicities, particularly COPD exacerbations, were not found. This is remarkable in a population in which over 40% of patients had pre-diagnosed COPD after lung resection, where postoperative exacerbations of COPD were reported to be frequent [29]. Instead, we noticed a significant improvement of FEV_1 – at least in the CPx arm. A similar effect was also noted by Pinson and Klastersky [30], although their population consisted of patients with advanced NSCLC and small cell lung cancer in which improvements of pulmonary function might be attributed to the reduction of tumour volume and/or reopening of obstructed airways. The effect on FEV_1 observed in our adjuvant-treated patients cannot be fully explained, especially the differences between treatment arms. One element may be the different rates of COPD between treatment arms, so that more patients with clinically non-overt exacerbation could have improved in the CPx arm. Another might be the use of dexamethasone for rash prophylaxis in the CPx arm, which theoretically might have influenced obstructive airway disease. The significant FVC increase is most probably due to ongoing postoperative recovery – an effect frequently perceived in the clinical context and already described elsewhere [28].

Several authors have reported a decrease of DLCO after chemotherapy [10, 12, 28]. However, we did not observe a significant change in DLCO after chemotherapy in the total group. Yet, in the CVb arm, DLCO decreased markedly in contrast to patients measured in the CPx arm. This might be attributed to the small numbers of patients where follow-up data on DLCO exist. However, for vinorelbine, toxic pulmonary side effects have been reported [14, 15], while data for pulmonary toxicity of pemetrexed are only casuistic [22]. Therefore, it cannot be excluded that the small differences in the changes of DLCO observed might be related to different toxic effects of the two drugs or their combination with cisplatin.

Our study has limitations. First, pulmonary functional changes in the different treatment arms have to be interpreted with caution as doses of chemotherapy differed between the arms. While patients under CPx received 90% of the doses planned, patients under CVb received only about 65%. Therefore, it cannot be excluded that with higher doses, especially in the CVb arm, more

marked changes could have been observed. Next, follow-up data could not be generated for all patients. Baseline pulmonary function tests, which were required as an inclusion parameter for admission to the study, should have been performed at all centres. However, despite being a mandatory requirement of the study protocol, due to the different policies of the centres, refusal by some patients and ongoing chemotherapy-induced adverse effects and deaths, not all baseline and follow-up pulmonary function tests were performed at all study sites in all patients. Therefore, a potential bias cannot be excluded, especially as loss of follow-up data more frequently occurred in patients in the CVb arm, where feasibility rates were lower and haematological toxicities were higher than in the CPx arm. As in our protocol adjuvant therapy administration had to be initiated 4–6 weeks after surgery and baseline lung function had to be tested within 14 days prior to chemotherapy, lung function might still have been impaired in some patients, probably concealing a decrease of lung function [12].

Additionally, scheduled time intervals between baseline and follow-up PFTs differed in both arms. For CPx the planned interval on treatment was 12 weeks, while it was 16 weeks for CVb. Yet, due to chemotherapy-related toxicities actual times on treatment differed (11.2 weeks for CPx vs. 9.9 weeks for CVb) between the arms, causing different intervals between baseline and follow-up PFT. This might have led to a bias, potentially contributing partially to the differences observed between arms, as mentioned above. Another important point is a lack of control patients resulting from the study design. To this consideration, in a study of patients following major lung resection without adjuvant therapy, Brunelli et al. [12] reported an increase of DLCO from discharge time to 3 months after surgery, suggesting that chemotherapy might have negatively influenced the improvement of DLCO and some lung function parameters, such as FVC or FEV₁. However, the data presented here report on a 30-day follow-up, at which point DLCO and other parameters were still impaired in the Brunelli et al. [12] cohort.

Conclusion

In conclusion, the present study provides evidence that adjuvant chemotherapy does not have a negative effect on pulmonary function. However, a non-significant difference between DLCO decline in different therapy arms warrants further study.

Appendix

Collaborators

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Acknowledgements

The trial was funded by unrestricted grants from Eli Lilly and Company, Germany, and Medac GmbH, Wedel, Germany. All authors contributed significantly to the manuscript and made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, drafted the submitted article or revised it critically for important intellectual content; and provided final approval of the version to be published. M.K. serves as a guarantor of the manuscript.

Financial Disclosure and Conflicts of Interest

This work was supported by unrestricted grants of Eli Lilly and Company, Germany and by Medac GmbH, Wedel, Germany. The financial sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript. M.T. received consulting honoraria, M.T., N.R. and F.G. served on boards for Lilly, F.G. and M.T. received travel support from Lilly and N.R. and F.G. received payment for lectures, including service on speaker's bureaus. J.V. and M.T. received research funding from Eli Lilly. The other authors declare no conflicts of interest.

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