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# A randomised multicentre phase II study with cisplatin/docetaxel vs oxaliplatin/docetaxel as first-line therapy in patients with advanced or metastatic non-small cell lung cancer

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**Background:** This study was designed to compare cisplatin/docetaxel with oxaliplatin/docetaxel in patients with advanced and metastatic non-small lung cancer as a first-line treatment.

**Methods:** Patients were randomly assigned to receive either cisplatin 75 mg m<sup>-2</sup> and docetaxel 75 mg m<sup>-2</sup> every 3 weeks or oxaliplatin 85 mg m<sup>-2</sup> and docetaxel 50 mg m<sup>-2</sup> every 2 weeks. The primary end point was response rate, and secondary end points were toxicity, time to progression and overall survival.

**Results:** A total of 88 patients (median age: 65 (39–86) years; stage IV: 93%) were randomly assigned. Response rate (complete and partial response) was 47% (95% CI: 33–61%) in the cisplatin/docetaxel arm and 28% (95% CI: 17–43%) in the oxaliplatin/docetaxel arm ( $P=0.118$ ). There was no significant difference in time to progression (6.3 vs 4.9 months,  $P=0.111$ ) and median overall survival (11.6 vs 7.0 months,  $P=0.102$ ) with cisplatin/docetaxel vs oxaliplatin/docetaxel, although slight trends favouring cisplatin were seen. Oxaliplatin/docetaxel was associated with significantly less (any grade) renal toxicity (56% vs 11%), any grade fatigue (81% vs 59%), complete alopecia (76% vs 27%), any grade leukopenia (84% vs 61%) and grade 3/4 leukopenia (44% vs 14%) and neutropenia (56% vs 27%).

**Conclusion:** Oxaliplatin/docetaxel has activity in metastatic non-small cell lung cancer, but it seems to be inferior to cisplatin/docetaxel.

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Despite encouraging efforts towards individualised and targeted therapies (Mok *et al*, 2009) in advanced non-small cell lung cancer (NSCLC), platinum-containing combinations still represent the standard of care for the majority of patients.

Cisplatin is widely used and is accepted as the most efficacious platinum compound; however, its use is limited by its toxicity profile, especially nausea/vomiting and nephrotoxicity. In addition, the complexity of cisplatin administration prohibits the use in a substantial proportion of patients, particularly elder patients and those with relevant comorbidities.

Although carboplatin seems to be an alternative to cisplatin, there is still a debate about the inferiority of carboplatin in terms of response rate (Rosell *et al*, 2002), progression and overall survival, deriving from several meta-analyses or head-to-head comparisons (Ardizzoni *et al*, 2007). Furthermore, carboplatin has a relevant haematologic toxicity profile when used in equipotent dosages.

In metastatic lung cancer, survival is modestly improved with platinum-based palliative chemotherapy, but, more important it can help to reduce tumour-related symptoms, and lead to improved quality of life (QoL). Hence, response often correlates with improved QoL, especially in patients with tumour-related symptoms (Fosella *et al*, 2003). On the other hand, chemotherapy-associated toxicity can outweigh the benefits resulting from tumour response. Therefore, there is enormous need to improve tolerability of chemotherapy without loss of efficacy.

Oxaliplatin, a third-generation platinum compound, proved to be effective in colorectal and gastric cancer, and has a favourable toxicity profile as compared with cisplatin (Al-Batran *et al*, 2008a). Furthermore, oxaliplatin can be safely given in an outpatient setting without need for specific hydration treatment.

In the first-line treatment of advanced NSCLC, oxaliplatin has been shown to have promising efficacy and a favourable toxicity profile in combination with pemetrexed (Scagliotti *et al*, 2005), gemcitabine (Bidoli *et al*, 2007) or docetaxel (Raez *et al*, 2006).

Based on these data, we designed this open-label, randomised, multicentric, phase II study to evaluate the efficacy and tolerability of oxaliplatin/docetaxel (Ox/Doc) in comparison with cisplatin/docetaxel (Cis/Doc) in stage IIIB/IV NSCLC.

## MATERIALS AND METHODS

**Patient eligibility.** Patients with histologically confirmed stage IIIB or IV (UICCC 6) NSCLC were eligible. Further criteria were as follows: no prior palliative chemotherapy, measurable target lesion, age over 18 years, Eastern Cooperative Oncology Group performance status  $\leq 2$ , sufficient bone marrow function, creatinine clearance  $> 45 \text{ ml min}^{-1}$  or serum creatinine  $\leq 1.25 \text{ ULN}$ , no concurrent uncontrolled medical illness and no other current or previous malignancy within the past 5 years (with the exception of squamous-cell carcinoma of the skin treated by surgery). Patients were excluded from the study if they had received neoadjuvant or adjuvant chemotherapy within the past 6 months; radiation therapy within the past 28 days; peripheral neuropathy of National Cancer Institute grade  $\geq 2$  at baseline; significant weight loss ( $> 10\%$  body weight in the preceding 6 weeks); brain metastases; inflammatory bowel disease; cardiomyopathy or cardiac insufficiency (New York Heart Association classification of heart disease class II to IV); known hypersensitivity to cisplatin, oxaliplatin or docetaxel; or were pregnant or breast-feeding. Women of child-bearing potential were advised to take adequate precautions to prevent pregnancy. Written informed consent was obtained from all patients. The study was approved by the ethics committees of the participating institutions.

**Treatment.** Patients were stratified by centre and performance status and were randomly assigned to either cisplatin/docetaxel

(arm A) or oxaliplatin/docetaxel (arm B). Patients in the arm A received cisplatin  $75 \text{ mg m}^{-2}$  as a 2-h infusion and docetaxel  $75 \text{ mg m}^{-2}$  as a 1-h infusion every 3 weeks. Patients in arm B received oxaliplatin  $85 \text{ mg m}^{-2}$  as a 1-h infusion and docetaxel  $50 \text{ mg m}^{-2}$  as a 1-h infusion every 2 weeks. Antiemetic prophylaxis was given according to guidelines. While receiving cisplatin, patients were hydrated with up to 3000 ml of normal saline. Treatment in arm A was continued up to six cycles and in arm B up to 8 cycles or until disease progression, unacceptable toxicity, patient's refusal or physician's decision. The addition of bevacizumab was allowed at the investigators' discretion. Patients were additionally stratified according to the planned use of bevacizumab.

The dose of docetaxel was reduced by 25% for diarrhoea and mucositis (exceeding National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 2) at first occurrence and by 50% at second occurrence. For grade 4 neutropenia/ thrombocytopenia or febrile neutropenia, the dose of the chemotherapy was reduced by 25% at first occurrence and 50% at second occurrence, and treatment was terminated by further occurrence. Cisplatin was discontinued for NCI-CTC grade 2 or worse renal toxicity. Oxaliplatin dose modifications were performed as described previously (Louvret *et al*, 2002).

**Toxicity assessment.** Toxicities were graded according to NCI-CTC version 3. Peripheral sensitive neuropathy was graded according to an oxaliplatin-specific scale as described previously (Caussanel *et al*, 1990)

**Evaluation of efficacy outcomes.** Responses were classified according to RECIST. Computed tomography or magnetic resonance imaging scans of target areas were performed before the start of the treatment and were repeated every 8 weeks in both arms. Patients who discontinued the study were evaluated every 2 months. Time to progression (TTP) was measured from the date of random assignment until disease progression. Overall survival (OS) was measured from the date of random assignment until death of any cause.

**Statistical analysis.** The primary end point was response rate according to RECIST 1.0 (Fisher's exact test). Secondary end points were toxicity ( $P$  for trend test), TTP (log-rank test), and OS (log-rank test). Survival data were calculated using the Kaplan–Meier method on the intent-to-treat (ITT) population, which was predefined as all randomly assigned patients with NSCLC (efficacy population). The safety analysis included all patients who received chemotherapy (safety population). According to Simons optimal two-stage design for clinical trials, calculated sample size with the assumption of a lower response rate of 30% and a difference of 15% was 81. Expecting a drop-off at a rate of  $\sim 10\%$ , we decided to enrol 88 patients in total.

## RESULTS

**Patients.** Between September 2008 and October 2010, a total of 88 patients (arm A, 43 patients; arm B, 45 patients) were recruited from 13 centres in Germany. Two patients were excluded from the efficacy population because of ineligible diseases (one patient with metastatic urothelial carcinoma of the urinary bladder and another with a mediastinal germline tumour). Therefore, 86 patients (arm A, 43 patients; arm B, 43 patients) were eligible for the efficacy analysis on an ITT basis. Overall, 87 patients were evaluable for the safety analysis. Fifteen patients, 7 patients in arm A and 8 patients in arm B, received additionally bevacizumab.

The two groups were well balanced for pretreatment characteristics (Table 1) except for sex, with the proportion of female patients being 48.8% in arm A and 62.8% in arm B

Table 1. Patient characteristics

	Cis/Doc (n = 43)		Ox/Doc (n = 45)	
	No. of patients	%	No. of patients	%
Total no. of patients	43	48.9	45	51.1
<b>Age</b>				
Median	65		65	
Range	47–86		39–82	
<b>Gender</b>				
Male	21	48.8	28	62.2
Female	22	51.2	17	37.8
<b>ECOG</b>				
0–1	40	93.0	40	88.9
2	3	7.0	5	11.3
<b>Histological subtype</b>				
Squamous cell	10	23.3	11	24.4
Adenocarcinoma	29	67.4	26	57.8
Other	4	9.3	8	17.8
<b>Stage</b>				
IIIB	3	7.0	2	4.4
IV	40	93.0	43	95.6
<b>Number of involved organs</b>				
≤1	19	44.2	15	33.3
2	15	34.9	19	42.2
≥3	9	20.9	11	24.4
Bevacizumab	7	16.3	8	17.8
Abbreviations: Cis/Doc = cisplatin/docetaxel; Ox/Doc = oxaliplatin/docetaxel; ECOG = Eastern Cooperative Oncology Group.				

(not significant). For both groups, median age was 65 years and median Eastern Cooperative Oncology Group performance status was 1. The majority (94.2%) of the patients had stage IV (metastatic) disease (arm A, 93%; arm B, 95.3%) and 61.2% had adenocarcinoma (arm A, 65.1%; arm B, 58.1%).

**Safety and toxicity.** The overall median treatment duration was 3.5 months (range, 0.2–6.3 months), with 3.3 months for arm A and 3.6 months for arm B. The median cumulative docetaxel dose per patient was 280 mg m<sup>-2</sup> without difference in the treatment arms (270 vs 290 mg m<sup>-2</sup>). The median cumulative doses per patient for cisplatin and oxaliplatin were 340 and 350 mg m<sup>-2</sup>, respectively.

Overall, 87 patients were assessable for toxicity (Table 2). The treatment was generally well tolerated, and the incidence of grade 3 to 4 toxicities was relatively low in the two treatment arms. There were no remarkable differences in the incidence of anaemia, thrombocytopenia, nausea, emesis, infections and peripheral sensory neuropathy between the treatment arms. However, significantly fewer patients experienced any grade leukopenia (84% vs 61%,  $P=0.03$ ) or grade 3/4 leukopenia (44% vs 14%,  $P=0.002$ ) and neutropenia (56% vs 27%,  $P=0.0091$ ) after treatment with Ox/Doc as compared with Cis/Doc. Furthermore, the rates of complete alopecia (76% vs 27%,  $P<0.0001$ ) and any grade renal function impairment (56% vs 11%,  $P<0.0001$ ) or fatigue (81% vs 59%,  $P=0.0344$ ) were significantly higher in cisplatin-treated patients. Grade 3/4 infections had a strong trend to occur more frequently with Cis/Doc (26% vs 9%,  $P=0.0507$ ).

Serious adverse events considered at least possibly related to the treatment were observed in 61% of patients treated with Cis/Doc and in 45% of patients treated with Ox/Doc (no significant difference).

Treatment delays occurred in 26 (60.5%) of 43 patients in arm A and 27 (61.4%) of 44 patients in the arm B (no difference). Dose reductions of any drug were required in 16 (37.2%) patients treated with Cis/Doc and in 12 (27.3%) patients treated with Ox/Doc.

Reasons for treatment discontinuation in the Cis/Doc and Ox/Doc arms, respectively, were disease progression (23.3% vs 22.7% of patients), death (7.0% vs 13.6%), toxicity (16.3% vs 2.3%,  $P=0.0298$ ), consent withdrawal (7.0% vs 11.4%) and other reasons (4.7% vs 4.0%).

The need for G-SCF support was significantly higher in arm A (12 vs 4 pts,  $P=0.0335$ ), as was the use of NK-1 antagonists (40 vs 12 pts,  $P=0.0001$ ).

Similar rates for antibiotic treatment or transfusion were observed in both treatment arms.

**Efficacy.** The median follow-up time for surviving patients was 7 months. Sixty-six patients (76.7%) had experienced progressive disease and 61 patients (70.9%) had died. The response rate, which was the primary end point, was in favour of Cis/Doc, with 47% (95% CI: 32.5–61.0%) vs 28% (95% CI: 16.6–42.8%) with Ox/Doc, but this did not reach statistical significance ( $P=0.118$ ; Table 3). There was no statistically significant difference in median OS and TTP with 11.6 vs 7.0 months ( $P=0.102$ ) and 6.3 vs 4.9 months ( $P=0.111$ ) with Cis/Doc and Ox/Doc, respectively, although the study was not powered to detect differences in survival (Figure 1). The 1-year survival rates were 32.5% (95% CI: 20.4–47.6%) with Cis/Doc and 18.6% (95% CI: 9.5–32.9%) with Ox/Doc and were also not significantly different ( $P=0.216$ ).

In the univariate analysis, there was no difference in OS and TTP regarding different subgroups such as sex, age, performance status and use of bevacizumab, with the exception of histology; in squamous-cell carcinoma, OS was significantly prolonged compared with nonsquamous histology ( $P=0.0448$ ), especially in the patient group receiving cisplatin. This unexpected observation may have derived from the limited patient number.

In the multivariate analysis, histology (squamous vs nonsquamous) and treatment (cisplatin vs oxaliplatin) were independent prognostic parameters for OS and TTP, whereas the gender and the use of bevacizumab did not correlate with survival (data not shown).

## DISCUSSION

Several noncomparative phase II studies have indicated that oxaliplatin doublets may represent an effective and well-tolerated first-line treatment for patients with advanced NSCLC (Monet *et al*, 2002; Franciosi *et al*, 2003; Kouroussi *et al*, 2003; Winegarden *et al*, 2004; Capuzzo *et al*, 2005; Raez *et al*, 2006; Früh *et al*, 2008; Mir *et al*, 2009; Radhakrishnan *et al*, 2009).

In a randomised setting, clinical efficacy of oxaliplatin doublets were similar to those with carboplatin in two phase II studies (Bidoli *et al*, 2007, gemcitabine combination; Scagliotti *et al*, 2005, pemetrexed combination) and had a more favourable toxicity profile. However, in one phase III trial (Weismann *et al*, 2011) comparing oxaliplatin/gemcitabine with carboplatin/paclitaxel, the incidence of adverse events exceeded the expected threshold, and hence the study was terminated early. Also, this trial showed similar efficacy for both treatment arms (response rates 15.2% vs 22.4%, median OS 9.90 vs 9.24 months).

In direct comparison to cisplatin, three trials are reported, one in combination with gemcitabine (Li *et al*, 2011) and two in combination with vinorelbine (Gao *et al*, 2005; Zhang *et al*, 2005),

Table 2. Main toxicities according to the National Cancer Institute Common Toxicity Criteria version 3 (treatment-related toxicities)

	All grades					Grade 3/4				
	Cis/Doc (n = 43)		Ox/Doc (n = 44)		P-value	Cis/Doc (n = 43)		Ox/Doc (n = 44)		P-value
	No.	%	No.	%		No.	%	No.	%	
<b>Haematologic</b>										
Anaemia	33	76.7	30	68.2	NS	1	2.3	5	11.4	NS
Leukopenia	<b>36</b>	<b>83.7</b>	<b>27</b>	<b>61.4</b>	<b>0.0300</b>	<b>19</b>	<b>44.2</b>	<b>6</b>	<b>13.6</b>	<b>0.0020</b>
Neutropenia	31	72.1	26	59.1	NS	<b>24</b>	<b>55.8</b>	<b>12</b>	<b>27.3</b>	<b>0.0091</b>
Thrombocytopenia	14	32.6	7	15.9	NS	4	9.3	0	0	0.0554
<b>Gastrointestinal</b>										
Nausea	39	90.7	38	86.3	NS	10	23.6	10	22.7	NS
Vomiting	25	58.1	22	50	NS	6	14	2	4.5	NS
Diarrhoea	28	65.1	25	56.8	NS	8	18.6	4	9.1	NS
Constipation	12	27.9	8	18.2	NS	0	0	0	0	NS
Stomatitis	24	55.8	17	38.6	NS	4	9.3	1	2.3	NS
<b>Hepatic</b>										
AST/ALT	7	16.3	15	34.1	NS	1	2.3	2	4.5	NS
ALP	7	16.3	9	20.5	NS	0	0	1	2.3	NS
<b>Neurologic</b>										
Neurosensory	23	53.5	27	61.4	NS	1	2.3	2	4.5	NS
<b>Others</b>										
Alopecia	38	88.4	31	70.5	NS	<b>33</b>	<b>76.4</b>	<b>12</b>	<b>27.3</b>	<b>&gt;0.0001</b>
Fatigue	<b>35</b>	<b>81.4</b>	<b>26</b>	<b>59.1</b>	<b>0.0344</b>	9	20.1	9	20.5	NS
Creatinine	<b>24</b>	<b>55.8</b>	<b>5</b>	<b>11.4</b>	<b>&gt;0.0001</b>	1	2.3	1	2.3	NS
Weight loss	18	41.9	12	27.3	NS	1	2.3	0	0	NS
Infection	18	41.9	13	29.5	NS	11	25.6	4	9.1	0.0507
Fever	10	23.6	8	18.2	NS	0	0	0	0	NS

Abbreviations: Cis/Doc = cisplatin/docetaxel; Ox/Doc = oxaliplatin/docetaxel; AST/ALT = aspartate aminotransferase/alanine aminotransferase; ALP = alkaline phosphatase; NS = not significant. Bold numbers indicate statistically significant differences.

all in Asian patients (and full publications only in Chinese), and hence our study is the only randomised trial conducted in a western patient population.

The motivation to conduct a trial replacing cisplatin by oxaliplatin includes the assumption that oxaliplatin is better tolerated than cisplatin. In this context, one may question the combination of two potential neurotoxic drugs in our trial. However, the feasibility of the combination of docetaxel and oxaliplatin was intensively explored by our group in multiple trials in advanced or metastatic gastric cancer and was found to be safe and tolerable, particularly with respect to neurotoxicity. In two phase III trials (one of them of our group), oxaliplatin at 85 mg m<sup>-2</sup> every 2 weeks proved to be at least as effective as cisplatin at standard doses for oesophagogastric cancer (Cunningham *et al*, 2008; Al-Batran *et al*, 2008a). In a next step, we conducted a phase II study adding docetaxel (50 mg m<sup>-2</sup> every 2 weeks) to our oxaliplatin-based doublet (FLO) (Al-Batran *et al*, 2008b). Although the observed toxicity was higher than known from the two-drug regimen, the treatment was feasible and generally well tolerated. Especially, the neurotoxicity was lower than expected, with higher-grade neurosensory toxicity rate of 9.3%. The results could be confirmed in multiple further trials (Al-Batran *et al*, 2011, 2012). Encouraged by these results in gastric cancer, we designed our current study using the present doses and the bi-weekly schedule in analogy to metastatic gastric cancer. The bi-weekly schedule used in our trial contains dose intensities of oxaliplatin (85 mg m<sup>-2</sup> every 2 weeks equivalent to

Table 3. Response rate				
	Cis/Doc (n = 43)		Ox/Doc (n = 43)	
	No.	%	No.	%
RR*	20	47 <sup>a</sup>	12	28
CR	1	2	1	2
PR	19	44	11	26
SD	12	30	15	35
PD	3	7	11	26
NE	8	19	5	12

Abbreviations: Cis/Doc = cisplatin/docetaxel; Ox/Doc = oxaliplatin/docetaxel; CR = complete response; PR = partial response; RR = response rate; SD = stable disease; PD = progressive disease; NE = not evaluable.  
<sup>a</sup>Cis/Doc: 95% CI (confidence interval): 0.3251-0.6109; Ox/Doc: 95% CI: 0.1663-0.4281.\*P-value = 0.1178.

42.5 mg m<sup>-2</sup> per week) and docetaxel (50 mg m<sup>-2</sup> every 2 weeks equivalent to 25 mg m<sup>-2</sup> per week) that are comparable to the doses generally recommended for 3-week schedules (oxaliplatin 130 mg m<sup>-2</sup> and docetaxel 75 mg m<sup>-2</sup>). However, it cannot be ruled out that the differences in toxicities and efficacy observed in our study might be related to an underdosing of these drugs or to this particular schedule.



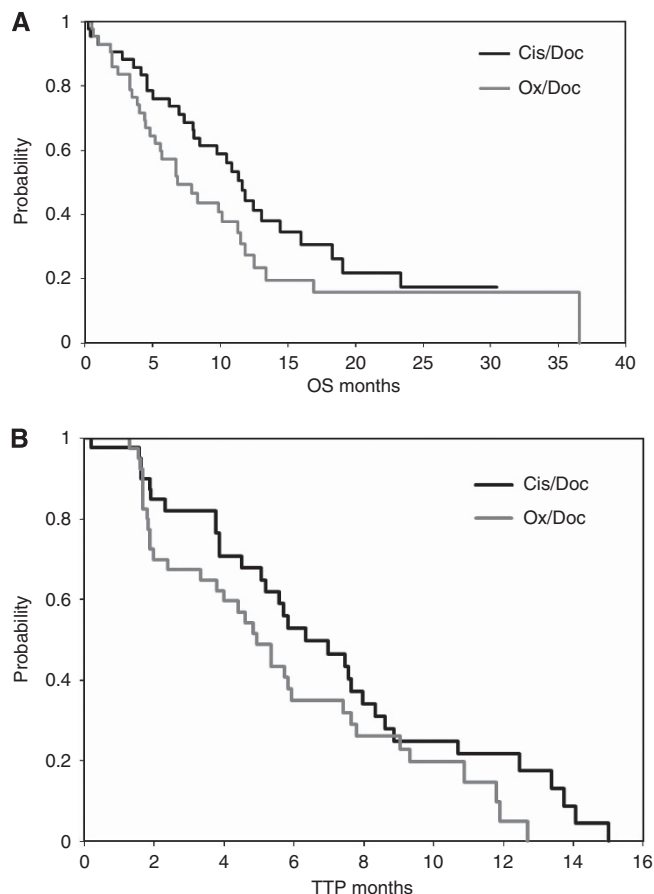


Figure 1. Survival analysis Kaplan–Meier curves for (A) OS and (B) TTP, assessed in the entire population. Median OS was 11.6 vs 7.0 months and median TTP 6.3 vs 4.9 months with cisplatin/docetaxel vs oxaliplatin/docetaxel, respectively.

In our multicentre study, we could demonstrate that the combination of oxaliplatin and docetaxel in the present dose and schedule is an active regimen in the first-line setting of metastatic NSCLC with an acceptable overall response rate of 28% (95% CI: 16.6–42.8%). The results are in line with other trials reporting response rates for oxaliplatin doublets from 15 to 50%. For example, Raez *et al* (2006) reported a response rate of 37% (90% CI: 22–55%) with oxaliplatin and docetaxel.

Although the response rate in our study was lower compared with the standard arm cisplatin/docetaxel with 47% (95% CI: 32.5–61.1%), the difference was not statistically significant ( $P=0.118$ ). However, it demonstrates that the combination of cisplatin and docetaxel is one of the most potent regimens in NSCLC in terms of response.

Regarding TTP (4.9 vs 6.3 months) and OS (7.9 vs 11.6 months), there was a trend in favour of the cisplatin combination; however, the difference did not meet statistical significance ( $P=0.127$  for TTP and  $P=0.139$  for OS). The 1-year survival rate in the oxaliplatin arm was considerably lower (18.6%, 95% CI: 9.5–32.9%) compared with other oxaliplatin-doublet trials. This may be influenced by the entire study population, as in the cisplatin arm the rate was only 32.5% (95% CI: 20.4–47.6%), which is in the lower range reported for cisplatin doublets. In the univariate and multivariate analyses, we observed a significant correlation of squamous-cell histology with improved overall survival. This could be a result of a higher efficacy of docetaxel in this histological subgroup, but this has to be interpreted with caution because of the limited patient number in our study.

Our study could show that toxicity is significantly reduced by the oxaliplatin doublet concerning nephrotoxicity (for all grades  $P=0.0001$ ) and severe grade leukopenia/neutropenia ( $P=0.002$  and  $P=0.009$ ). Furthermore treatment discontinuation because of toxicity occurred significantly less frequently with oxaliplatin/docetaxel. Additionally, there was a trend towards a reduced infection rate ( $P=0.0507$ ), although this did not reach statistical significance. Patients with lung cancer often have infectious complications because of their comorbidities as well as cancer-related disventilation of the lung regardless of the specific treatment. This may have contributed to similar infection rates in both arms despite reduction of leukopenia/neutropenia. Furthermore, patients with cisplatin/docetaxel received more frequently G-CSF support, and this additionally may have influenced the febrile neutropenia/infection rate.

Relevant side effects of cisplatin such as nausea, emesis and loss of appetite were not reduced by oxaliplatin. However, NK-1-antagonists (aprepitant) were significantly more often used in cisplatin-treated patients and may have contributed to this result.

In addition, higher-grade fatigue and anaemia, which are often limiting factors in treatment, were not influenced by the use of oxaliplatin. Interestingly the incidence of sensoric neuropathy was not different in both treatment arms.

Our study shows that the oxaliplatin/docetaxel combination seems to have some activity in the first-line treatment of metastatic non-small lung cancer. However, the extent of activity observed in our trial does not justify further evaluation in a phase III setting. The study also shows that some reduction of toxicity was observed, mainly with respect to nephrotoxicity and leukopenia/neutropenia, as expected. However, this alone also does not justify further evaluation of oxaliplatin for particular groups such as patients unable to receive a cisplatin-based combination, because for this setting, especially in terms of reduction of non-haematological side effects, carboplatin is a well-established alternative for cisplatin, as shown in numerous randomised phase II and III studies. Furthermore, other standard options such as non-platinum doublets or single-agent chemotherapies are also acceptable alternatives for these patients.

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