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A randomised phase II study of docetaxel/oxaliplatin and docetaxel in patients with previously treated non-small cell lung cancer: An Alpe–Adria Thoracic Oncology Multidisciplinary group trial (ATOM 019)

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ABSTRACT

Introduction: To date, no combination regimen has proven superior to single agent chemotherapy as a second-line treatment for non-small cell lung cancer (NSCLC).
Methods: This multicenter, non-comparative randomised phase II trial evaluated the activity of docetaxel (75 mg/m^2 on day 1) with oxaliplatin (70 mg/m^2 on day 2) every 3 weeks in previously treated NSCLC patients; the reference arm was single-agent docetaxel (75 mg/m^2 on day 1 every 3 weeks). It was designed as a one-stage, three-outcome phase II trial; 21 evaluable patients were required in each arm. The primary end-point was response rate; secondary end-points were toxicity, progression free survival (PFS) and overall survival.
Results: Fifty patients were enrolled. Patient characteristics included male/female, 76/24%; median age 62 years; ECOG PS 0/1, 36/64%; previous platinum-based chemotherapy, 98%. Partial response was seen in 20% and 8%, stable disease in 52% and 32%, of patients treated with docetaxel/oxaliplatin and docetaxel, respectively. Main grade 3–4 toxicities were neutropenia 56% and 64%; febrile neutropenia 4% and 8%; diarrhoea 12% and 4% for docetaxel/oxaliplatin and docetaxel, respectively. Median PFS was 5.0 and 1.7 months, median survival 11.0 and 7.1 months, and 1-year survival 44% and 32% for docetaxel/oxaliplatin and docetaxel, respectively.
Conclusions: The study met its pre-defined study end-point; docetaxel/oxaliplatin and more generally platinum-containing doublets warrant further evaluation as second-line therapy for patients with NSCLC.

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2. Introduction

Second-line treatment options for patients with advanced stage non-small cell lung cancer (NSCLC) include single agent chemotherapy with either docetaxel or pemetrexed, and treatment with one of the oral tyrosine kinase inhibitors erlotinib and gefitinib.[1] Whatever the treatment, the response rate is less than 10% and the prognosis remains poor with a median survival of 6–7 months, justifying the evaluation of new regimens in this setting. Strategies currently under investigation include the use of doublets, the re-challenge with a platinum compound and the combination of a molecularly targeted agent with standard treatments.

The absence of cross-resistance with cisplatin/carboplatin[2–4] and favourable toxicity profile, along with evidence of activity in NSCLC both in preclinical[5] and clinical studies[6] make oxaliplatin a good candidate for combination regimens in this disease. Several phase II studies have evaluated the use of oxaliplatin doublets first-line in NSCLC patients, with response rates ranging between 13% and 48% and an acceptable toxicity.[7] In a phase II study the combination of oxaliplatin and docetaxel achieved an encouraging response rate of 37% and was associated with a mild toxicity profile in 29 chemo-naïve patients with NSCLC[8]; to date, this combination has not been evaluated in the second-line setting.

In this multicenter, non-comparative, open label, randomised phase II study, we evaluated the activity of docetaxel and oxaliplatin in patients with advanced NSCLC previously treated with chemotherapy. The doses and schedule for docetaxel and oxaliplatin are based on the results of a phase I study in patients with metastatic breast cancer or NSCLC who had not received chemotherapy for advanced disease.[9]

3. Patients and methods

3.1. Patient eligibility

Main inclusion criteria were: histologically or cytologically proven, stage IIIB (wet) or IV NSCLC; disease progression after one prior chemotherapy; age $\geqslant$18 and <70 years; ECOG performance status (PS) of 0 or 1; measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST)[10]; adequate bone marrow (absolute granulocytes neutrophils count $>1.5\times10^9$/L; platelets $\geqslant100\times10^9$/L; haemoglobin $\geqslant$10 g/dL), hepatic (total bilirubin $\leqslant$ upper limit of normal (ULN); transaminases $\leqslant$ 2 times ULN; alkaline phosphatase $\leqslant$ 2 times ULN) and renal (creatinine $\leqslant$ 1.5 times ULN, CrCl > 60 mL/min) function; no contraindication to steroid therapy. Patients with brain metastases were eligible, provided symptoms were controlled for $\geqslant$4 weeks after surgery and/or radiation therapy, and on stable or reducing dose of steroids at the time of study entry. Exclusion criteria included: > 1 line of chemotherapy; prior chemotherapy with docetaxel or oxaliplatin; New York Heart Association Class 3 or 4 heart disease, myocardial infarction within 6 months, or other clinically significant, uncontrolled, concomitant illness; peripheral neuropathy grade >1; previous cancer except curatively treated cervical carcinoma *in situ* and non-melanoma skin cancer.

The study was approved by the local Ethics committee at each of the participating centres and conducted according to Good Clinical Practice. All patients provided written informed consent. This study was registered in the EudraCT database (EudraCT 2004-002539-25).

The study protocol was developed during the 6th Joint FECS/AACR/ASCO Workshop on Methods in Clinical Cancer Research – Flims, Switzerland in 2004.

3.2. Treatment

At registration, patients were randomised 1:1, without stratification, to receive docetaxel (75 mg/m^2) on day 1 and oxaliplatin (70 mg/m^2) on day 2 in the experimental arm or docetaxel (75 mg/m^2) on day 1 in the reference arm. Treatment was given intravenously as an outpatient and repeated every 3 weeks for up to 6 cycles in the absence of progressive disease, unacceptable toxicity or patient refusal.

All patients received premedication with prednisone 50 mg orally, twice daily for 3 days, starting one day prior docetaxel administration. Prophylactic anti-emetic therapy, including 5-hydroxytriptamine 3 receptor antagonists and steroids was recommended for patients treated with docetaxel/oxaliplatin. Dose modifications for toxicity were predefined. Granulocyte-colony stimulating factor was permitted for the management of febrile neutropenia but not for prophylactic use.

3.3. Assessment of response and toxicity

Baseline chest and abdominal computed tomography (CT) scans were performed within 4 weeks before enrolment. Brain CT scan and bone scan were performed only as clinically indicated. Response was assessed every other cycle according to RECIST version 1.0.[10] Patients who went off treatment in the absence of progression underwent disease evaluation every 2 months until progression or death. Responses were confirmed by an independent radiologist, who was blind to the treatment received by the patient.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0. Haematological toxicity was assessed weekly; in case of treatment delay >2 weeks, the patient went off study.

3.4. Statistical considerations

The primary end-point of this open-label, investigator-initiated, randomised phase II study was response rate (RR). Secondary end-points were toxicity, progression free survival (PFS) and overall survival (OS).

The study was designed as a one-stage three-outcome phase II trial,[11] with Ho: RR $\leqslant$ 10% and HA: RR $\geqslant$ 30%. The type I and type II error rates were set at 5% and 10%, respectively. The probabilities of correctly rejecting an ineffective treatment, or of correctly accepting an effective treatment were both set at $\geqslant$80%. Twenty-one patients evaluable for response were required in the experimental arm. If <4 responses were observed, the combination was to be declared

ineffective; if ⩾5 responses were observed, the combination was to be declared effective and worth further investigation; if four responses were observed, the phase II trial was inconclusive. The original design[11] was adapted by the incorporation of non-comparative randomisation to standard treatment with docetaxel to facilitate the interpretation and validation of the primary end-point.

Differences in baseline variables between the two groups were assessed using unpaired 2 tailed Student's t-test, Fisher's exact test and Mann Whitney test. PFS and OS curves were produced for all patients (intention-to-treat analysis) using the Kaplan–Meier method; Cox proportional hazards model was used to estimate hazard ratios. The software used for these analyses was GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA).

4. Results

4.1. Patient characteristics

Between January 2005 and May 2008, 50 patients were enroled at four Italian centres, affiliated with the ATOM (Alpe–Adria Thoracic Oncology Multidisciplinary group trial) group (Fig. 1). At data cut-off (March 1st, 2010), 48 of the 50 patients enroled had died, 24 (96%) in each arm; follow-up for the two patients still alive was 32.2 and 22.4 months.

Patient and disease characteristics were balanced between the two arms (Table 1), with the exception of a higher proportion of patients having PS 0 in the experimental docetaxel/oxaliplatin arm ($p = 0.04$), and more younger patients in the reference docetaxel arm ($p = 0.03$); there was a non-significant trend for a longer interval since previous chemotherapy in the docetaxel/oxaliplatin arm ($p = 0.18$).

4.2. Treatment

A total of 108 and 77 cycles were administered in the docetaxel/oxaliplatin and docetaxel arms, respectively. The median number of cycles was 4 in the docetaxel/oxaliplatin (range 2–6) and 2 in the docetaxel arms (range 1–6). In the experimental arm, the mean dose intensity for docetaxel was 22.1 mg/m^2/week (88% of that planned) and for oxaliplatin was 20.7 mg/m^2/week (89%); in the reference arm, the mean dose intensity for docetaxel was 22.7 mg/m^2/week (91%).

Dose reductions were required in 12 (48%) and eight (32%) patients, and treatment delays ⩾7 days in eight (32%) and six (24%) patients in the docetaxel/oxaliplatin and docetaxel arms, respectively. Unresolved toxicity was the reason for treatment delay in four and three cases, respectively; in the remaining cases, delay was due to patients' requests to postpone the treatment or delays in performing the evaluation CT

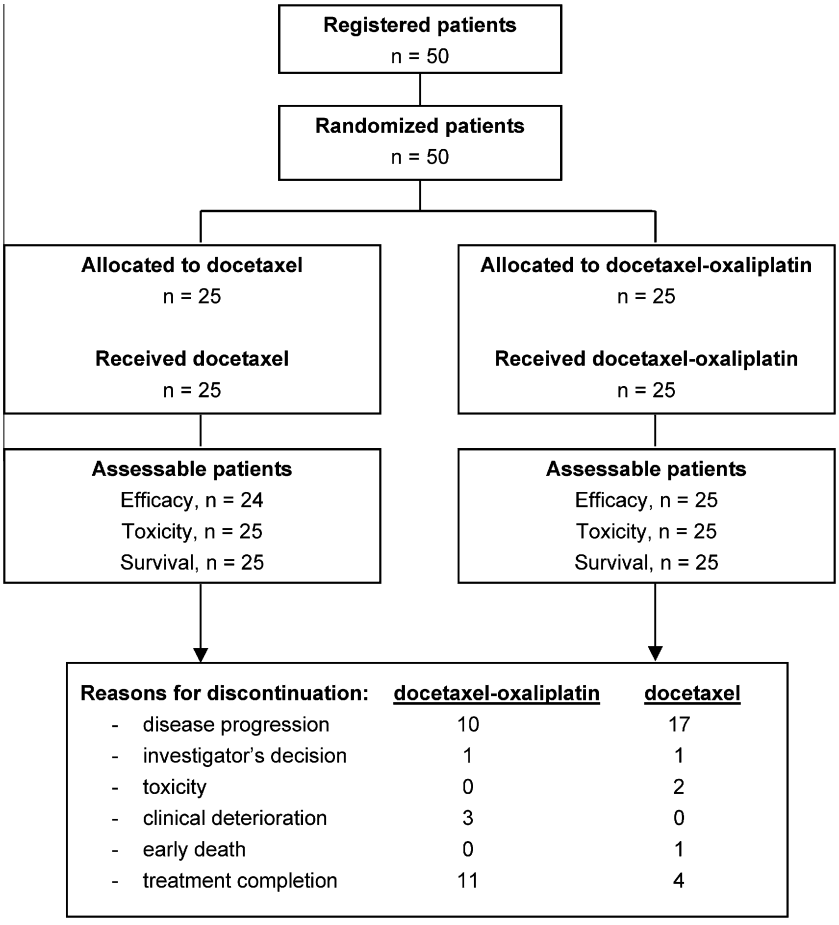

Fig. 1 – CONSORT diagram showing the progress of patients through the trial, adapted from Begg et al.[12]

Table 1 – Patient demographics and baseline characteristics.

Parameter	Docetaxel + oxaliplatin $n = 25$	Docetaxel $n = 25$	All $n = 50$
Age, years			
Median	63	60	62
Range	53–69	44–69	44–69
Gender, n (%)			
Male	18 (72)	20 (80)	38 (76)
Female	7 (28)	5 (20)	12 (24)
Performance status, n (%)			
0	13 (52)	5 (20)	18 (36)
1	12 (48)	20 (80)	32 (64)
Histology, n (%)			
Adenocarcinoma	10 (40)	9 (36)	19 (38)
Squamous cell carcinoma	5 (20)	5 (20)	10 (20)
Large cell carcinoma	1 (4)	0 (0)	1 (2)
NSCLC, NOS	9 (36)	11 (44)	20 (40)
Stage, n (%)			
IIIB	3 (12)	2 (8)	5 (10)
IV	22 (88)	23 (92)	45 (90)
Site of disease, n (%)			
Lung	23 (92)	24 (96)	47 (94)
Lymph nodes	18 (72)	20 (80)	38 (76)
Bone	7 (28)	7 (28)	14 (28)
Brain	5 (20)	4 (16)	9 (18)
Liver	5 (20)	7 (28)	12 (24)
Adrenals	4 (16)	3 (12)	7 (14)
Prior treatment, n (%)			
Platinum based chemotherapy	25 (100)	24 (96)	49 (98)
Erlotinib	1 (4)	0 (0)	1 (2)
Time since previous chemotherapy, n (%)			
$\leqslant$ 6 months	12 (48)	18 (72)	30 (60)
> 6 months	13 (52)	7 (28)	20 (40)

scan. Reasons for treatment discontinuation are reported in Fig. 1.

4.3. *Response to treatment*

All 25 patients were evaluable for response in the docetaxel/oxaliplatin arm, as were 24 (96%) of those in the docetaxel arm (Table 2); the remaining patient was not evaluable due to early death.

Table 2 – Best overall response.

Best response	Docetaxel + oxaliplatin $n = 25$	Docetaxel $n = 25$
ORR, *n* (%)	5 (20)	2 (8)
95% CI	6.8–40.7	1.0–26.0
CR, *n* (%)	0 (0)	0 (0)
PR, *n* (%)	5 (20)	2 (8)
SD, *n* (%)	13 (52)	8 (32)
CR + PR + SD, *n* (%)	18 (72)	10 (40)
PD, *n* (%)	7 (28)	14 (56)
Not evaluable	0 (0)	1 (4)

ORR, overall response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

There were no complete responses (CR). There were five and two partial responses (PR) in the docetaxel/oxaliplatin and docetaxel arms, respectively; this corresponds to overall RR of 20% (95% CI 6.8–40.7) and 8% (95% CI 1.0–26.0), respectively. Stable disease (SD) was the best response in 52% and 32% of patients in the docetaxel/oxaliplatin and docetaxel arms, respectively; the clinical benefit rates (CR + PR + SD) were 72% and 40%, respectively. Three of the five patients who achieved a partial response and five of the 13 patients who had stable disease in the experimental arm had an interval since prior platinum-based chemotherapy > 6 months. A higher proportion of patients had progressive disease as their best response in the docetaxel arm than in the combination arm (56% and 28%, respectively).

4.4. *Toxicity*

All patients were evaluable for toxicity, which was manageable and as expected (Table 3). In both arms, the most frequent grade 3–4 toxicity was neutropenia (56% and 64% in the combination and single arm, respectively).

Table 3 – Summary of treatment-related toxicity per patient across all cycles.

Adverse event	Number (%) of patients			
	Docetaxel + oxaliplatin (*n* = 25)		Docetaxel (*n* = 25)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Haematologic				
Anaemia	21 (84)	0 (0)	21 (84)	0 (0)
Neutropenia	18 (72)	14 (56)	20 (80)	16 (64)
Thrombocytopenia	4 (16)	0 (0)	5 (20)	0 (0)
Febrile neutropenia	1 (4)	1 (4)	2 (8)	2 (8)
Non-haematologic				
Nausea	14 (56)	0 (0)	11 (44)	3 (12)
Vomiting	8 (32)	0 (0)	4 (16)	1 (4)
Diarrhoea	15 (60)	3 (12)	6 (24)	1 (4)
Fatigue	22 (88)	2 (8)	19 (76)	1 (4)
Peripheral neuropathy	15 (60)	0 (0)	13 (52)	0 (0)

There were no treatment related deaths. Toxicity was the reason for treatment discontinuation only for two patients, both in the docetaxel arm (grade 3 diarrhoea and hyperbilirubinemia, respectively).

4.5. *Survival*

Median PFS was 5.0 months and 1.7 months for patients in the docetaxel/oxaliplatin and docetaxel arm, respectively (Fig. 2A). Median OS was 11.0 months in the docetaxel/oxaliplatin arm, with a 1-year survival rate of 44%; in the docetaxel arm, median OS was 7.1 months, with a 1-year survival rate of 32% (Fig. 2B).

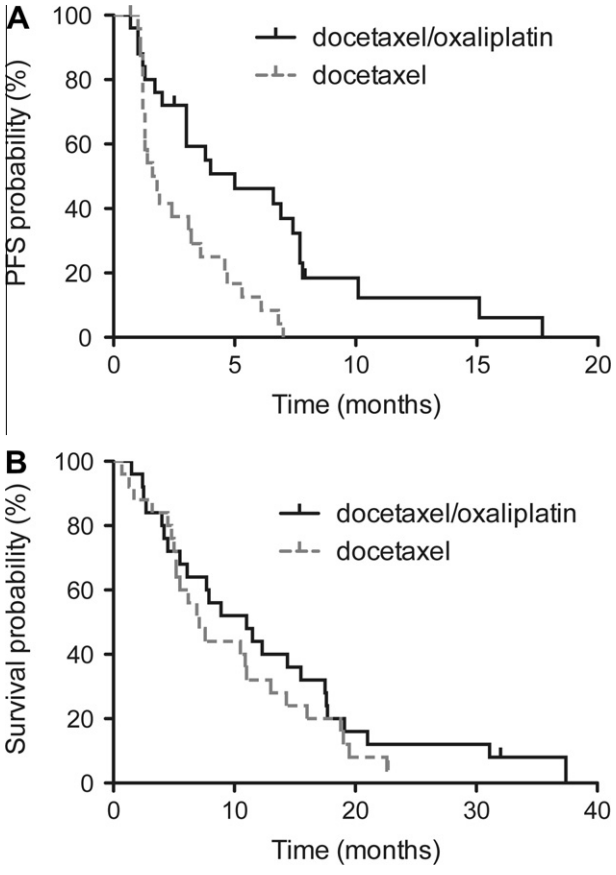

Fig. 2 – Kaplan–Meier curves for progression free survival (A) and overall survival (B).

4.6. *Post-study systemic treatment*

Twelve patients (48%) in the docetaxel/oxaliplatin arm and 14 patients (56%) in the docetaxel arm received post-study systemic treatment for NSCLC; it was erlotinib in most of these cases (100% and 78% in the docetaxel/oxaliplatin and docetaxel arm, respectively); two patients in the docetaxel arm subsequently received third-line chemotherapy (carboplatin/paclitaxel and single agent pemetrexed, respectively).

5. Discussion

This is the first randomised trial to evaluate an oxaliplatin-containing doublet in patients with advanced NSCLC previously treated with chemotherapy. This study demonstrates that the combination of docetaxel/oxaliplatin is active in this setting and the toxicity profile is manageable.

Until recently, combination regimens in second-line treatment of NSCLC have mainly been investigated in small, single-arm, phase II trials, with only occasional increase in RR, and rarely an apparent increase in PFS or OS.[13–17] In the last few years, several studies, a few randomised, have consistently reported more encouraging RR and PFS.[18] This may reflect greater activity of those combination regimens, but clinical factors may also have contributed; in particular patients receiving second-line treatment may be fitter than in the past. This is due to a combination of advances in imaging that allow earlier detection of disease progression after first-line chemotherapy, a greater willingness by oncologists to institute second-line treatment even in asymptomatic patients, and improvements in supportive therapy that have made combination regimens more tolerable.

A recent randomised trial investigated the re-challenge with a platinum-based doublet as a second-line treatment for patients with NSCLC[19]; in that phase II study, 240 patients with disease progression following a platinum-based chemotherapy were randomised 1:1 to pemetrexed (500 mg/m^2) and carboplatin (AUC 5) or single agent pemetrexed (500 mg/m^2) every three weeks. Time to progression, the primary endpoint, was longer for carboplatin/pemetrexed, 4.2 months versus 2.8 months (HR 0.67, 95% CI 0.51–0.89, $p = 0.005$). The RR was 17% for carboplatin/pemetrexed and 6% for single agent pemetrexed.[19] No significant difference was observed in terms of OS (median OS was 7.6 and 8.0 months for carboplatin/pemetrexed and pemetrexed, respectively; HR 0.85, 95% CI 0.63–1.2). Both treatments were well tolerated, with grade 3–4 toxicity limited to fatigue and haematological toxicity, more frequent in the combination arm and overall manageable. Those results are consistent with the ones we report here, suggesting a possible role for the re-challenge with a platinum-based doublet in these patients.

The combination of docetaxel/oxaliplatin was well tolerated, with no significant increase in grade 3–4 toxicities with the addition of oxaliplatin. The good toxicity profile may be related with the exclusion of patients with PS > 1 and older than 70. Only two patients discontinued treatment due to toxicity, both in the docetaxel arm. No grade 3–4 peripheral neuropathy was recorded in the combination arm, despite previous treatment with cisplatin (92% of patients) or other neurotoxic chemotherapy such as paclitaxel or vinorelbine (24%). This may be explained in part by the eligibility criteria having required any baseline neurotoxicity to be grade 0 or 1. In addition, the planned dose intensity of oxaliplatin was just 23.3 mg/m^2/week, substantially lower than that in regimens associated with significant neurotoxicity, e.g. 42.5 mg/m^2/week in the FOLFOX3 or FOLFOX4 colorectal cancer regimens.[20] The combination of pemetrexed and carboplatin was also well tolerated but is less attractive in second-line treatment as pemetrexed appears to benefit only NSCLC patients with non-squamous histology[21] and was recently approved in the first-line setting for such patients.

In conclusion, the combination of docetaxel/oxaliplatin has an encouraging activity and a manageable toxicity profile in patients with previously treated NSCLC; these results support further evaluation of this combination. More generally, doublets that incorporate re-challenge with a platinum compound should be evaluated in this setting.

Disclosures

GF and FG have received honoraria from Sanofi-Aventis.

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Conflict of interest statement

None declared.

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