Docetaxel and Intermittent Erlotinib in Patients with Metastatic Non-small Cell Lung Cancer; A Phase II Study From The Hellenic Cooperative Oncology Group

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Abstract. *Aim: To determine the more effective dosing sequence of intermittent erlotinib and docetaxel for treating chemotherapy-naive patients with advanced Non-Small Cell Lung Cancer (NSCLC). Patients and Methods: Patients were randomized to receive daily erlotinib for 12 consecutive days prior to docetaxel (Arm A) or after docetaxel (Arm B). Progression-free survival (PFS) was the primary end-point; secondary end-points were overall survival (OS) and objective response rate (ORR). Results: Fifty eligible patients received a total of 226 treatment cycles (median: 3). Median PFS and OS were 3.6 months and 10.5 months, respectively (differences were not statistically significant between the two arms). Neutropenia grade 3 and 4 occurred in 15 patients, while two patients developed grade 3 diarrhea. There were two treatment-related deaths (pulmonary embolism and non-neutropenic sepsis). Conclusion: Intermittent administration of erlotinib does not appear to improve the clinical outcome of single-agent docetaxel chemotherapy in unselected patients with NSCLC in the first-line setting.*

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Lung cancer is the leading cause of death from cancer worldwide; 60% of patients with lung cancer will die within one year from diagnosis and less than 15% will survive for two years. The majority of patients with Non-Small Cell Lung Cancer (NSCLC) exhibit advanced stage disease that is not amenable to curative treatment (1). Platinum and non-platinum combination chemotherapy appears to have been plateaued in efficacy and newer therapeutic agents have added an incremental benefit in specific sub-sets of patients (1, 9, 10, 13).

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs), erlotinib and gefitinib, have been licensed for the treatment of patients with NSCLC who have active *EGFR* mutations, in which cases these compounds can offer significant improvement of clinical outcome (3, 11). In addition, erlotinib has been approved for treatment in

NSCLC patients with *EGFR* wild-type tumors who have failed first-line chemotherapy, showing similar efficacy to single-agent chemotherapy in this setting (2).

Single-agent activity of EGFR TKIs led to investigation of the agents with conventional cytotoxic chemotherapy, which failed to improve efficacy over-chemotherapy only in patients with metastatic lung cancer of the non-small cell histology type. EGFR TKIs, were combined with platinum-based chemotherapy in the first-line setting, but failed to demonstrate additional benefit (7, 8). One explanation is antagonism due to TKI-induced G_1 arrest, reducing cell cycle-dependent activity of chemotherapy. Therefore, alternative ways of administration may help to overcome this adverse effect. Solit *et al*. found that when paclitaxel was combined with pulsatile gefitinib it was significantly superior to continuous dosing (15). Two days of gefitinib treatment before paclitaxel was most effective, causing greater tumor regression and a higher percentage of complete responses than other schedules. In clinical grounds, high-dose erlotinib given for two days before carboplatin/paclitaxel administration was shown to produce the highest response rate and longest survival, when compared to low dose erlotinib given before chemotherapy or high dose given after chemotherapy (12). In a similar approach, Sangha *et al*., found that intercalated schedules of erlotinib with docetaxel chemotherapy are feasible and tolerable and can achieve pharmacodynamic separation.

We initiated this phase II randomized trial to determine the most effective dosing sequence of intermittent erlotinib and docetaxel for treating patients with the diagnosis of advanced NSCLC. The trial was registered at clinicaltrials.gov (NCT00783471).

Patients and Methods

Patients. The Institutional review boards of the participating centers approved the study. The study was also approved from the National Organization for Medicine. Both erlotinib and docetaxel were provided free of charge by Roche and Sanofi, Athens, Greece, respectively. Male and female patients aged 18 to 75 years inclusive, with histologically confirmed metastatic NSCLC who had not been previously treated with anticancer drugs for advanced disease were considered eligible for enrollment in this trial. Patients signed informed consent for the study, as well as for the use of their biological material in research. Other eligibility criteria were performance status (PS) of 0-1 and adequate hematologic, renal and hepatic function. An interval of at least 4 weeks since any prior major surgery or extended-field radiotherapy was mandatory for study entry. Patients who had received prior chemotherapy for advanced NSCLC or who had received prior treatment targeting the epidermal growth factor axis (*i.e*. erlotinib, gefitinib, cetuximab, or transtuzumab) were excluded. Patients were also excluded if they had symptomatic brain metastases or spinal cord compression that had not been definitively treated with surgery and/or radiation; previously diagnosed and treated patients with brain metastases or spinal cord compression with evidence of stable disease for at least 2 months were allowed to enter the study.

Treatment. This was a multi-center, randomized, phase II trial. Eligible patients were randomized to receive treatment with erlotinib for 12 consecutive days prior to docetaxel (Arm A) or after docetaxel (Arm B). Erlotinib was taken orally at a dose of 150 mg every day for 12 consecutive days and docetaxel was administered intravenously at a dose of 75 mg/m^2. A two-day wash out period was introduced between the two drugs, as shown in the treatment schema (Figure 1). Treatment cycles were repeated every 21 days. No dose escalation of either erlotinib or docetaxel was permitted. Anti-emetics and dexamethasone pre-medication to prevent hypersensitivity reactions were administered according to individual Institutional guidelines.

Number of patients/study duration. Approximately 110 patients (55 per study arm) with stage IV NSCLC, chemotherapy-naive, were planned to be enrolled in this study. A minimum of 12 months recruitment with 6 months follow up for PFS from randomization was anticipated. Patients would continue on treatment until completion of eight cycles or disease progression, or unacceptable toxicity or withdrawal of patients' consent, whichever occurred first. Patients' follow-up will continue until disease progression or death, whatever occurs first. The trial will end when all patients have relapsed or died.

Toxicities and dose modifications. In the presence of grade 2 or higher hematologic or non-hematologic toxicity, therapy was deferred until toxicity resolved to a maximum of grade 1. In the event of grade 4 hematological toxicity, the docetaxel dose was reduced to 60 mg/m^2, while erlotinib was reduced to 100 mg/d in cases of grade 3 skin rash, mucositis or diarrhea. These dose reductions were maintained in all subsequent cycles. Grade 1 to 2 erlotinib-related diarrhea was managed with loperamide. Erlotinib-related rash was managed at the discretion of the investigator. Prophylactic filgrastim or pegfilgrastim were not allowed.

Within 2 weeks following a dose reduction, erlotinib-related toxicity should have improved to National Cancer Institute-Common Terminology Criteria grade 2. If not, further dose reductions by one level were required. Dosing could be interrupted for a maximum of 2 weeks, if clinically indicated or the toxicity was not controlled by optimal supportive medication. Once a patient had a dose reduction for toxicity, the dose was not be re-escalated except for erlotinib-related rash. In the event of a rash, dose could be re-escalated when rash was grade 2 or less. If patients required a dose interruption of more than 2 weeks, erlotinib treatment was discontinued and the patient was taken off the study.

Evaluation of response. Response assessments were performed after 6 weeks of treatment, and then every 6 weeks during treatment and every 3 months thereafter. Response was assessed according to the Response Criteria for Solid Tumors (RECIST, Version 1.1) by two expert radiologists (AKF, PM).

EGFR and KRAS testing. Mutational analysis for *EGFR* and *KRAS* was not obligatory for study entry. However, DNA was extracted from paraffin-embedded tumors obtained retrospectively from the HeCOG Tumor Repository Bank, Thessaloniki, Greece. Mutational analyses for both genes were conducted as previously described (11) at the Laboratory of Molecular Oncology, Hellenic Foundation for Cancer Research, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece.

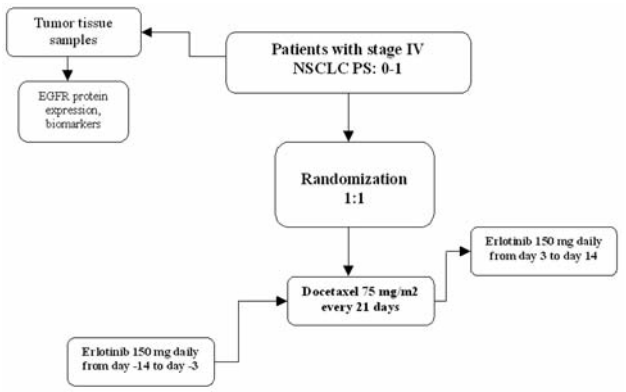

Figure 1. *Study schema. Eight cycles were to be completed unless disease progression, unacceptable toxicity, death, or withdrawal of patient's consent occurred.*

Statistical considerations. Eligible patients were randomized at a ratio of 1:1.The randomization lists were produced using random permuted blocks.

Primary end-point: PFS was the primary end point of this trial and was estimated by the Kaplan-Meier method. PFS was defined as the time interval from the day of randomization until progression of disease (PD) during treatment or death by any cause, whichever occurred first. Disease progression was defined according to the RECIST criteria.

Secondary end-points: Secondary end points of this study were OS and ORR in patients of each arm. Response was assessed according to the RECIST criteria. PFS and ORR were defined in subgroups according to the EGFR mutational status and smoking history.

Comparisons between groups were made using the log-rank test, while the estimated curves were presented by the Product Limit method (Kaplan-Meier plot). A Cox proportional hazards model adjusting for the commonly accepted prognostic factors was used to fit PFS. The results are presented as the point estimate of the hazard ratio (HR) accompanied by the 95% confidence interval (CI) for this estimation.

Sample size calculation was based on the hypothesis that the PFS hazard ratio between the two arms would be 1.8 over a baseline median PFS of 9 months. A sample of 55 patients per arm provided 80% power at the 10% alpha level for a two-sided log-rank test. However, the study was terminated prematurely due to the low accrual rate, as well as a lower than expected treatment effectiveness of both arms.

Results

Baseline characteristics. Between November 2008 and November 2009, 51 patients were enrolled and randomly assigned to receive treatment in the two arms at the different collaborative oncology Centers. The study was terminated early because the accrual was slow. One patient was found ineligible and was not included in the analysis due to abnormal lab values prior to the first day of treatment, which was a violation of one of the inclusion criteria. Baseline characteristics by treatment arm are listed in Table I. There were no statistically significant differences with regard to age, sex, performance status and sites of metastases. Numerically, there were 3 patients with brain metastases in

Table I. *Patients' characteristics*.

		Group	
		Arm A	Arm B
Patients	N	25	25
Age	Median	64	61
	Min-Max	47-74	43-74
Gender	Male	19 (76%)	20 (80%)
	Female	6 (24%)	5 (20%)
PS (ECOG)	0	12 (48%)	14 (56%)
	1	13 (52%)	11 (44%)
Histology type	Adenocarcinoma	12 (48%)	17 (68%)
	Large cell		1 (4%)
	Squamous cell	6 (24%)	3 (12%)
	Mixed	1 (4%)	
	Undifferentiated	2 (8%)	
	Unclassified	2 (8%)	2 (8%)
	Missing	2 (8%)	2 (8%)
Histology grade	2	1 (4%)	5 (20%)
	3	14 (56%)	10 (40%)
	4	1 (4%)	
	Missing	9 (36%)	10 (40%)
Smoking status	Former smoker	8 (32%)	7 (28%)
	Never smoker	3 (12%)	2 (8%)
	Smoker	14 (56%)	16 (64%)
Number of metastatic sites	1-3	21(84%)	20 (80%)
	>3	4 (16%)	5 (20%)

Randomized: n=51, ineligible: 1, eligible: 50.

Table II. *Response to chemotherapy.*

		Group	
		Arm A	Arm B
Patients	N	25	25
Best overall response	PR	6 (24%)	3 (12%)
	SD	7 (28%)	15 (60%)
	PD	10 (40%)	4 (16%)
	Treatment discontinuation prior evaluation	2 (8%)	2 (8%)
	Early toxic death		1 (4%)

N, Number; PR, partial response; SD, stable disease; PD, progression of disease.

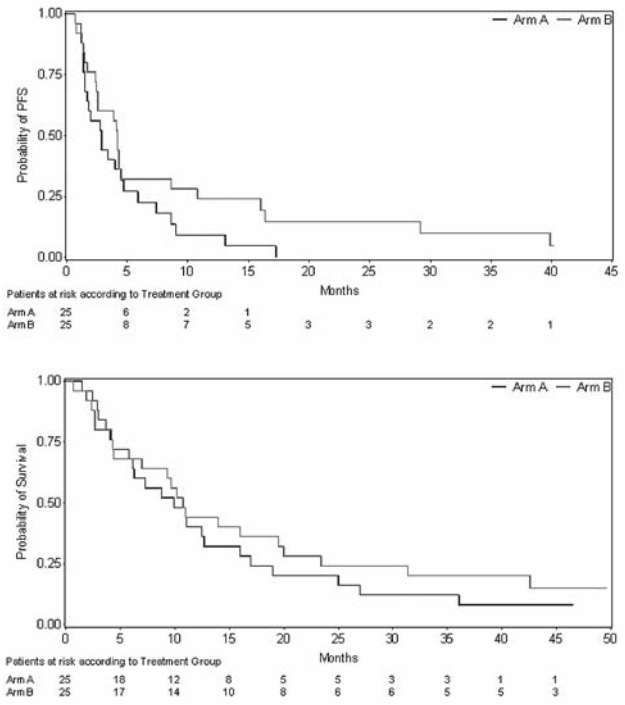

Figure 2. *PFS and OS by treatment arm.*

arm B. Thirty patients were current smokers, whereas 20 were former or never-smokers.

Treatment. Patients received a median of three cycles of treatment in each arm. A total of 226 treatment cycles were administered. There were no differences in the number of cycles of treatment administered between treatment arms. Five patients in arm A and eight patients in arm B received the maximum of eight cycles of treatment.

Efficacy. Activity outcomes are listed in Table II. No complete response (CR) was documented in either arm. In the cohort of patients treated with 150 mg erlotinib before docetaxel (Arm A), 6 patients (24%) had a documented partial response (PR) and 7 patients (28%) had stable disease (SD). In the cohort of patients treated with docetaxel followed by erlotinib (Arm B), 3 patients (12%) experienced PR and 15 patients (60%) had SD. No difference of objective response rates was observed between the two arms (p=0.46). In both arms, treatment was prematurely discontinued in 8% of patients before the first evaluation of response.

PFS and OS. PFS and OS results are presented in Tables III and IV. Overall, patients had a median PFS of 3.65 months. Patients treated in arm A had a median PFS of 2.9 months, whereas in patients treated in arm B, the median PFS was 4.2 months (difference not statistically significant) (Figure 2). Patients with adenocarcinoma histology had a trend of a better PFS (p=0.08). With regards to OS, the median was 10.5 months in all patients. Median survival in arm A was 9.9 months, while in arm B it was 10.8 months (difference not statistically significant) (Figure 2). Adenocarcinoma histology showed a better disease outcome (median OS 11 months, p=0.07).

Toxicity. All grade ≥3 toxicities are shown in Table V. Neutropenia grade 3 and 4 occurred in 8 patients (33%) in arm A and in 7 patients (27%) in arm B. Only grade 1 sensory neuropathy had occurred in 8.3% of patients in arm A and in 11.5% of patients in arm B. One patient in each arm developed grade 3 diarrhea, whereas grade 2 diarrhea occurred in two patients in each arm. One patient treated in arm A developed fatal pulmonary embolism and another patient treated in arm B died because of non-neutropenic sepsis. Patients treated in arm A developed more frequently anemia (50.0% *vs.* 11.5%, p<0.05) and skin rash (50.0% *vs.* 15.4%, p<0.001). Dose reductions were required in docetaxel; 28% of administered cycles in arm A and in 20% in arm B, which did not differ between the two arms (p=0.2). Considering erlotinib, the dose was reduced in 9% of administered cycles in arm A and 10.4% in arm B (p=0.8). One patient in arm B stopped treatment because significant exacerbation of psoriasis was developed.

Molecular characteristics. *EGFR* and *KRAS* mutational analysis was not mandatory for entry into the protocol. However, available archived biopsy material was collected from 37 patients. *EGFR* and *KRAS* mutation results were available for all 37 patients (Table VI). Active *EGFR* mutations were found in 9 patients; 5 patients were found to have the *L858* mutation. Patients with active *EGFR* mutations had a longer PFS compared with patients with non-active *EGFR* mutations and wild-type patients (9.00 months *vs.* 2.75 months); however this difference failed to reach statistical significance (p=0.09). Similar findings were observed for OS, which was 20.0 months in *EGFR* mutant patients, as opposed to 9.8 months in wild-type *EGFR* patients (p=0.18).

Subsequent systemic anticancer therapy. Out of the 50 patients enrolled in both arms, all but 2 patients who died early during the study, received second-line treatment for NSCLC. Most common treatments were platinum-plus-pemetrexed and other platinum combinations. Median PFS for second-line treatment was 4.7 months in arm A and 5.1 months in arm B. Many patients received several lines of subsequent therapy.

Table III. *PFS analysis by treatment group*.

					Range			95% CI			
		N	Failed	% censored	Min	Max	Median	LL	UL	% event free at 6 months	*p*-Value
All patients		50	47	6	0.70	36.70	3.65	2.40	4.30	27%	
Group	Arm A	25	24	4	0.70	17.30	2.90	1.50	4.50	23%	0.1443
	Arm B	25	23	8	0.70	36.70	4.20	2.50	8.60	32%	

LL, Lower confidence limit; UL, upper confidence limit.

Table IV. *OS analysis by treatment group*.

					Range			95% CI			
		N	Failed	% censored	Min	Max	Median	LL	UL	% event free at 6 months	*p*-Value
All patients		50	42	16	0.70	42.30	10.50	6.30	14.00	68%	
Group	Arm A	25	22	12	1.50	42.30	9.90	5.80	16.00	68%	0.4916
	Arm B	25	20	20	0.70	41.40	10.80	4.40	20.00	68%	

LL, Lower confidence limit; UL, upper confidence limit.

Table V. *Toxicity by treatment group (number of patients)*.

	Arm A Grade			Arm B Grade		
	3	4	5	3	4	5
Allergy/Immunology	.	.	.	1	.	.
Blood/Bone marrow	5	6	.	3	4	.
Cardiac general	1	.	.	.	.	.
Constitutional symptoms	1	.	.	2	.	.
Dermatology/Skin	.	.	.	1	.	.
Gastrointestinal	2	.	.	1	.	.
Infection	3	.	.	5	1	1
Metabolic/Laboratory	1	.	.	3	.	.
Neurology	.	.	.	4	1	.
Pain	.	.	.	1	.	.
Pulmonary/Upper respiratory	1	.	1	.	.	1
Renal/Genitourinary	.	.	.	.	1	.
Vascular	.	.	.	.	1	.
Cardiac arrythmia	.	.	.	1	.	.
Coagulation	.	.	.	1	.	.
Death	.	.	.	.	.	1

Table VI. *EGFR and KRAS Mutation Frequencies*.

Available mutation results in N=37	Frequencies	
	N	%
KRAS mutations		
WT	33	89.0
MUT	4	11.0
EGFR mutations (3 categories)		
WT	27	73.0
Active Mutations	9	24.0
Non-active Mutations	1	3.0
EGFR mutations (2 categories)		
WT/Non-active Mutations	28	76.0
Active Mutations	9	24.0

WT, wild-type; MUT, mutated.

Discussion

This randomized phase II study investigated a potential superiority between two mirrored schedules of separate consecutive erlotinib and docetaxel administrations on efficacy and toxicity. This schedule was based on promising pre-clinical data that demonstrated sequence specificity and schedule-dependent interactions of EGFR TKIs and chemotherapy, suggesting that strategies involving intermittent EGFR TKI dosing between chemotherapy cycles could achieve pharmacodynamic separation and better antitumor activity (15).

The study was stopped early due to low recruitment rates and because intermediate analysis showed that it could not achieve its primary end-point, which was to demonstrate a statistically significant difference in PFS between the two arms. Interestingly, partial remissions were numerically, but not statistically, higher in arm A, in which erlotinib preceded

the administration of docetaxel. This finding is in line with the results of Solit *et al*. who found that, in pre-clinical studies, two days of high-dose gefitinib before paclitaxel was most effective, causing significantly greater mean tumor regression and a higher percentage of complete responses than other schedules (15). Similarly Riely *et al*. found in their randomized phase II study of pulse erlotinib, before or after carboplatin and paclitaxel, that erlotinib dosed at 1,500 mg on days 1 and 2 before chemotherapy achieved better response rates and longer survival (12). Moreover, the median PFS in this study was 3.6 months, which lies between PFS observed with common first- and second-line treatments in unselected populations. It is possible that the prolonged administration of erlotinib at standard doses selected in this study could neither effectively produce the expected pharmacodynamic separation and sensitize tumors to cytotoxic chemotherapy, as modeled in preclinical studies (4), nor expose cancer cells to meaningful antitumor levels.

Therapy was well-tolerated in both treatment arms, with low recorded rates of hematological toxicity, diarrhea or skin rash being recorded. This is in contrast with data of studies that investigated concurrent with chemotherapy or single-agent administration of erlotinib. In the phase III TRIBUTE trial that investigated erlotinib combined with carboplatin and paclitaxel chemotherapy in advanced NSCLC, the incidence of grade 3 rash was 7.2% (6), while Shepherd *et al*. in a study that investigated erlotinib monotherapy in previously-treated NSCLC patients reported higher incidences of grade >2 of diarrhea and skin rash (14). This could partially be explained by the fact that erlotinib in our trial was given intermittently for 12 days within a 21-day treatment cycle.

Activating *EGFR* mutations were found in 9 out of the 37 tumor samples that were tested. These patients had longer PFS (9 months) and OS (20 months), compared to those having wild-type *EGFR*, as expected (3). However, differences in PFS and OS were not statistically significant, which is explained by the fact that the number of *EGFR* mutant patients was very low.

A strong weakness of the current study is the fact that a combination of a taxane with an anti-EGFR drug as first line treatment in patients with NSCL, turned to be inferior in virtue of response rates and PFS, compared with those achieved when treating wild type or unknown *EGFR* status patients with standard platinum doublets. Two issues should be pointed-out at this stage. First, at the time the study was conceived, *EGFR* testing was not prerequisite to offer a patient anti-EGFR treatment. Second, similar design trials, also called window-of-opportunity trials, have managed to identify beneficial molecular-targeted agents in several solid tumors, that might have been discarded if they would have been evaluated in later stages of diseases. Nevertheless, this is not yet the case in NSCLC, as the results of the TORCH trial showed that in unselected patients with advanced NSCLC, first-line erlotinib, followed at progression by cisplatin and gemcitabine, was significantly inferior compared to the reverse sequence (5). Overall, this was a negative study, showing that intermittent administration of erlotinib at standard doses over a period of several days does not appear to improve the clinical outcome of taxane chemotherapy in unselected patients. Whether brief pulsatile administration of high doses of EGFR inhibitors prior to chemotherapy can be more efficacious is still an unanswered question.

Conflicts of Interest

The Authors have no conflict of interest in regards to this study.

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