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A Phase II Study of Modulated-Capecitabine and Docetaxel in Chemonaive Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Introduction—This phase II single-arm trial of docetaxel and capecitabine in previously untreated non-small cell lung cancer (NSCLC) patients was designed to evaluate response rate of this regimen based on promising efficacy data from phase II testing in pre-treated NSCLC patients. The trial also evaluated the correlation between peripheral blood dihydropyrimidine dehydrogenase (DPD) expression and efficacy/toxicity.

Methods—Patients with advanced NSCLC (metastatic, including malignant pleural effusion) without prior chemotherapy were enrolled. Baseline DPD screening was performed; patients with baseline DPD level < 0.07 nmol/min/mg protein were considered ineligible for the study. Treatment included a 28-day cycle of docetaxel 36 mg/m² days 1, 8, 15 and capecitabine 1250 mg/m²/day in divided doses on days 5–18. Overall response rate (RR) was the primary endpoint with a target RR of 50%. Correlative studies included evaluation of DPD activity levels in peripheral blood and correlation with clinical responses.

Results—Twenty-eight patients received 86 cycles of treatment (median 3 cycles) and were evaluable for response. The RR was 18% (5 patients); RR did not meet the pre-specified efficacy endpoint and the trial was stopped. 14 patients had stable disease (SD - 50%) and 4 pts had SD > 12 weeks. Median time to progression was 3.3 months (95% CI 1.5 – 4.6 months). Median overall

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Conflict of Interest Statement

No conflicts of interest exist for the authors of the manuscript.

survival was 10.5 months (95% CI: 3.2 – 15 months). Main toxicities included fatigue, stomatitis and leukopenia. DPD levels ranged from 0.06 to 0.26 nmol/min/mg. The majority of responders (4/5) had DPD levels $\leq$ 0.1 nmol/min/mg. Most of the responders (4/5) experienced grade 3 toxicities including leukopenia, dehydration, fatigue, and diarrhea. None of the patients (0/4) with higher DPD levels (>0.2 nmol/min/mg) had a response.

Conclusion—The response rate for the regimen did not demonstrate sufficient activity and further study of this regimen in this setting is not indicated. Interestingly, the results suggest that low DPD expression may be associated with response to capecitabine but also with increased toxicity.

Keywords

non-small cell lung cancer; dihydropyrimidine deficiency; capecitabine

Introduction

Lung cancer is one of the most common and most lethal cancers with an estimated 222,520 new cases and 157,300 deaths in 2010 [1]. At diagnosis, most patients have advanced or metastatic disease. Despite the high mortality rate in advanced lung cancer, cytotoxic chemotherapy is associated with improved survival compared to best supportive care alone [2–4]. First line chemotherapy often utilizes platinum-based doublets [3]. Fluoropyrimidines have been studied in combination with platinum (particularly in Japan [5–8]) but these agents are not commonly used in treatment of non-small cell lung cancer (NSCLC) in the United States.

The oral fluoropyrimidine UFT (tegafur/uracil) in combination with cisplatin has demonstrated activity in NSCLC in phase II testing [8, 9]. Uracil acts as a substrate for dihydropyrimidine dehydrogenase (DPD) allowing slower degradation of tegafur and higher concentrations of the active metabolite 5-fluorouracil (5-FU) in the tumor.

Likewise, S-1 – a novel fluoropyrimidine combination – has also demonstrated activity in NSCLC. Phase I/II trials of S-1 as monotherapy and in combination with irinotecan have demonstrated promising results in Japan [10–12]. Like UFT, S-1 consists of a combination of tegafur with competitive inhibitors of DPD and orotate phosphoribosyltransferase that inhibits the phosphorylation of 5-FU in the gastrointestinal tract to reduce the serious gastrointestinal toxicity associated with 5-FU [13]. A phase III Japanese study comparing carboplatin with S-1 versus carboplatin with paclitaxel demonstrated the non-inferiority of the S-1 combination with a primary endpoint of overall survival. The median overall survival with S-1/carboplatin was 15.2 months (95% CI, 12.4 – 17.1) versus 13.3 months (95% CI, 11.7 – 15.1) in the paclitaxel/carboplatin arm (hazard ratio 0.928). Secondary endpoints included progression-free survival (PFS), response rate, and toxicity. PFS was similar for both combinations (S-1/carboplatin 4.1 months vs paclitaxel/carboplatin 4.8 months, HR 0.998, 95% CI 0.837–1.190). Although paclitaxel/carboplatin demonstrated a higher overall response rate (29.0% v 20.4%, $P = .019$), disease control rate was similar (73.5% v 71.7%, $P = .635$). Toxicity was variable – paclitaxel was associated with more neutropenia, febrile neutropenia, alopecia, and neuropathy whereas S-1 was associated with higher rates of thrombocytopenia, nausea, vomiting, and diarrhea. This trial demonstrated that the combination of carboplatin and S-1 is a reasonable regimen for first-line therapy of NSCLC [5].

Although UFT and S-1 are not available in the United States, capecitabine – also a 5-FU pro-drug – is approved and utilized breast and colorectal cancers. Capecitabine is converted into the active metabolite through a 3-step enzymatic process. The final enzyme is

thymidine phosphorylase (TP) – located at higher concentration in tumor tissues – which converts the prodrug into 5-FU [14]. The degradation of 5-FU depends on DPD; deficiency of this enzyme leads to significant toxicity from prolonged tissue exposure to 5-FU.

To improve the efficacy of capecitabine, it has been combined with other cytotoxic chemotherapy agents. Pre-clinical studies demonstrate altered expression of thymidine phosphorylase (TP) in tumor xenografts treated with taxanes and synergistic activity between capecitabine and docetaxel. The peak TP expression occurred between 4–8 days after administration of taxane [15]. To optimize the biologic activity of this combination, several trials of capecitabine and docetaxel evaluated alternative dosing regimens. A phase I trial of weekly docetaxel with capecitabine days 5–18 in solid tumors demonstrated tolerable toxicity and antitumor activity in NSCLC [16]. A phase II trial of the same regimen in previously treated NSCLC suggested that this regimen was well tolerated with reasonable response rate. In this trial, tumor expression of thymidine synthase (TS) and TP levels were also evaluated and the results suggested a possible correlation between tumor expression and response to therapy [17].

We report the results of a phase II trial of docetaxel and capecitabine as first line therapy in chemo-naïve patients with advanced stage NSCLC (NCT00201825). The primary aim of the study was to determine the objective response rate (complete and partial responses (CR, PR)); secondary aims were to evaluate time to tumor progression (TTP) and overall survival.

Materials and Methods

Eligibility

Patients with histologically confirmed advanced NSCLC who had not received prior chemotherapy were eligible to participate. Eligibility criteria also included the following: age ≥ 18 years; Eastern Cooperative Oncology Group performance status of 0–1; predicted life expectancy ≥ 12 weeks; adequate hematopoietic function (absolute neutrophil count 1500/mcl, hemoglobin > 9.0 gm/dl, platelets ≥ 100, 000/mcl); adequate renal and hepatic function (creatinine < 1.5 × upper limit of normal, serum bilirubin ≤ upper limit of normal, aspartate aminotransferase / alanine aminotransferase < 1.5 × upper limit of normal, alkaline phosphatase ≤ 2.5 × upper limit of normal). Patients with evidence of any active serious infectious process, peripheral neuropathy ≥ grade 1, history of myocardial infarction within the past 6 months, congestive heart failure requiring therapy, unstable angina, uncontrolled diabetes mellitus (defined as random blood sugar > 250 mg/dL), or psychiatric disorders that would interfere with consent or follow-up were excluded. Additional exclusion criteria included pregnant or lactating women, prior malignancy within the past 5 years prior to enrollment (except for non-melanoma skin cancer or *in situ* cervical carcinoma), patients with history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80, or untreated or symptomatic brain or leptomeningeal metastatic disease. Previously irradiated brain metastases which did not require corticosteroids for symptom control were permitted. If patients received radiation therapy, a 4-week period post-therapy was required prior to study treatment. Due to potential interactions between capecitabine and coumarin-based anticoagulants, patients requiring therapeutic doses of these drugs were not allowed on the study.

Prior to treatment, patients were screened for DPD deficiency due to the potential for severe or lethal toxicity after exposure to fluoropyrimidines in DPD deficient patients [18, 19]. A blood sample was obtained after consent, but prior to treatment initiation, and sent to a reference laboratory to assess for DPD levels. Patients with baseline DPD level < 0.07 nmol/min/mg protein were considered ineligible for the study.

All patients provided written informed consent approved by The Ohio State University Institutional Review Board.

Treatment Plan

As previously described, docetaxel was administered intravenously at 36 mg/m² over 30 minutes weekly on days 1, 8, 15 and capecitabine 1250 mg/m² per day - divided into 2 oral doses (625mg/m² per dose) on days 5 to 18 of every 28-day cycle[16].

Patients were pre-medicated with dexamethasone 8 mg for 3 doses (24 mg/week); this steroid regimen was based on previous studies of weekly docetaxel demonstrating low incidence of peripheral edema and hypersensitivity reactions [16, 17, 20]. Dexamethasone eye drops twice daily for three days were also used to decrease the potential for increased lacrimation with weekly docetaxel administration. Antiemetic and anti-diarrheal therapy was administered at the discretion of the investigator. Routine prophylactic use of colony-stimulating factor (G-CSF or GM-CSF) or erythropoietin was not permitted. Therapeutic use for patients with ANC < 500/uL for more than 5 days, febrile neutropenia, sepsis, or anemia was allowed at the investigator's discretion.

Dose modifications

Prior to initiation of a new cycle of therapy, an absolute neutrophil count 1500/mcl and platelets 100,000/mcl, and improvement of all other treatment related toxicity to grade 1 was required. A dose delay of up to 2 weeks was permitted (3 weeks if clinical benefit was documented); if the patient toxicities did not resolve after a treatment delay, the patient was removed from trial. Docetaxel dose modifications were made for grade 4 thrombocytopenia, neutropenic fever, liver dysfunction and non-hematologic toxicities grade 3. Capecitabine dose modifications were made for hand-foot syndrome grade 3 or 4, refractory nausea/vomiting (despite optimal anti-emetic therapy), and other non-hematologic toxicity grade 3.

Clinical Benefit Evaluation

Measurable disease was required for study enrollment. Baseline computerized tomography scans were done within 4 weeks of starting chemotherapy in all patients and repeated after every 2 cycles. Response Evaluation Criteria in Solid Tumors (RECIST) were used for assessment of tumor response. All responding patients were required to have their response confirmed 4 to 6 weeks after the first documentation of response. Time to progression (TTP) and overall survival (OS) were calculated from the date of the first docetaxel infusion.

Assessment of DPD levels

Peripheral blood sample for DPD assay was collected from all patients at time of enrollment and assay was performed prior to study treatment. To perform the assay, 60 milliliters of whole blood were obtained and separated to isolate peripheral blood mononuclear cells. Samples were flash frozen and shipped. All samples were analyzed by a central lab within one week of collection. The DPD radioassay was done as previously described [21]. PBMCs were isolated, suspended in buffer A (35 mmol/L potassium phosphate, 2.5 mmol/L magnesium chloride, and 10 mmol/L 2-mercaptoethanol; pH 7.4), and lysed by sonication. The protein concentration of PBMC cytosol was determined by a Bradford assay [22]. Approximately 250 µg of total protein was added to a reaction mixture containing 200 µmol/L of NADPH, buffer A, and 8.2 µmol/L of [6-¹⁴C] 5-FU (56 mCi/mmol) and incubated at 37°C for 30 minutes. One hundred and thirty-microliter aliquots of the reaction mixture were removed every 5 minutes and immediately placed into termination tubes containing an equal volume of ice-cold ethanol. Protein was precipitated by incubating the mixture at

–80°C overnight. The mixture was then thawed and filtered. [6-¹⁴C]-FUH₂ and [6-¹⁴C]-5-FU were separated by reverse phase high-pressure liquid chromatography and quantified using previously described methods [22]. The amount of [6-¹⁴C]-FUH₂ formed at each time point (*y* axis) was plotted against time (*x* axis), and the formation rate of [6-¹⁴C]-FUH₂ was computed. DPD enzyme activity was determined by dividing the [6-¹⁴C]-FUH₂ formation rate by the amount of total protein added to the reaction mixture. Results were reported as DPD level nmol/min/mg protein; < 0.20 nmol/min/mg protein on fresh specimens or < 0.07 nmol/min/mg protein on frozen specimens was considered ineligible for the study. DPD level was repeated on day 29 of the study.

Statistical analysis

The study utilized a Simon two-stage design with a primary endpoint of objective response rate. It was assumed that the regimen would be worthy of further study if the response rate was ≥ 50% (*p*₁); likewise, the combination regimen was considered ineffective if the true response probability was < 30% (*p*₀) based on prior NSCLC trials. Therefore a two-stage design of 28 and 39 patients, with power of 0.90 and a one-sided significance level of 0.10 was used in this study. If 7 or fewer patients demonstrated responses in the first 28 evaluable patients, the regimen would be terminated early and deemed ineffective.

DPD levels at day 0 and day 29 were compared by paired *t*-test. Since no significant difference was found, the averaged DPD level was used to classify patients into DPD low group (averaged DPD < 0.1 nmol/min/mg) or DPD high group (averaged DPD ≥ 0.1 nmol/min/mg). Associations between best responses and DPD level groups were reported and tested by Fisher's exact test. The Kaplan-Meier estimates of mean and median overall survival time in days were reported. Log-rank and Wilcoxon-Gehan tests were used to analyze the difference in overall survival time in days by DPD levels (high vs. low). Log-rank and Wilcoxon-Gehan tests were used to analyze the difference in progression free time in days by DPD levels (high vs. low).

Results

Patients Characteristics

Twenty-nine patients (22 males and 7 females) with a median age of 61 (range, 39–76) were enrolled and received treatment between December 2004 and November 2007 (table 1). One patient was not evaluable for response because the patient was removed from study after an adverse event (cardiac ischemia). The most common histology was adenocarcinoma (44%) followed by squamous cell carcinoma and poorly-differentiated NSCLC. Twenty-six patients (90%) had stage IV disease, while 3 patients (10%) had stage IIIB disease. Metastatic sites included lungs, liver, adrenal gland, brain, bone, and pleural/pericardial effusions. One patient was discovered at autopsy to have pancreatic adenocarcinoma metastatic to the lungs. A total of 28 evaluable patients received 86 cycles of therapy (median 3 cycles, range 1–7 cycles).

Toxicity

Expected toxicities were observed and were primarily grades 1 and 2. Grade 3 or 4 toxicities included fatigue/asthenia, anorexia, ascites, hemoptysis, dehydration, mucositis, vomiting, hand-foot syndrome, anemia, neutropenia, and leukopenia. No neutropenic fever or neutropenia with infection was reported. One serious adverse event was observed; a patient had a myocardial infarction after day 7 of cycle 1 and was removed from study. This patient was not evaluable for response. Fatigue, diarrhea, mucositis, and hand-foot syndrome/skin and nail changes were the most common toxicities. Please refer to tables 2 and 3 for detailed

toxicities. Six (21%) patients required dose-reduction for toxicity (mucositis, diarrhea, dehydration, nausea, neutropenia, and hand-foot syndrome).

Antitumor activity

The overall RR was 18% (5 of 28 patients) and did not meet the pre-specified RR to continue the study (8 responses required). All of the observed responses were PRs by RECIST criteria. In addition, 14 patients had stable disease (SD) (50%; 4 patients with SD > 12 weeks). Median TTP was 3.3 months (95% CI 1.5 – 4.6 months, figure 1). Nine patients (32%) had progressive disease (table 4).

Survival

The median OS was 10.5 months (95% CI, 3.2 – 15 months) as of 6/30/2010 (figure 2). At the time of censorship, 2 patients were still alive. Nineteen patients received second-line chemotherapy, 13 patients received third-line therapy, and 7 patients received 4 or more additional lines of therapy. Eleven patients also received radiation therapy after trial therapy. The most common second/third line therapies were erlotinib and pemetrexed; additional subsequent therapies included gemcitabine, platinum agents (cisplatin/carboplatin), and sorafenib.

Patient survival was analyzed according to DPD level (low vs. high) to determine if there was a difference in efficacy according to DPD expression. DPD level in peripheral blood was measured at baseline and on day 29 of therapy. Average DPD level was calculated using the day 0 (baseline) and day 29 DPD levels. Average DPD level was available in 27 of the 28 evaluable patients; 17 patients had average DPD level ≥ 0.1 nmol/min/mg (high) and 10 patients had average DPD level < 0.1 nmol/min/mg (low).

Both log-rank test (which puts equal weights for all time points) and the Wilcoxon-Gehan test (which puts equal weights for earlier time points) do not show significant difference between DPD low and high groups in terms of survival curves ($p=0.35$ and $p=0.12$). The non-parametric estimates of overall survival times show a trend of difference between the DPD level groups. However, due to small sample sizes and large proportion of censored data points in the later stage of the study, the test for difference in overall survival time is not significant.

Laboratory Correlates

Average baseline peripheral blood DPD level was 0.14 nmol/min/mg (range 0.064 – 0.26 nmol/min/mg). One patient was treated on study with a baseline DPD of 0.064 nmol/min/mg. Initially this patient was thought to meet eligibility criteria, however when the DPD level was subsequently reported, it was recognized that an error had been made. The patient had already tolerated a cycle of treatment, so a decision was made to allow the patient to continue on trial. This patient had SD as best response – time to progression was 7 weeks. This patient did not require any dose modifications or delays. Of the 5 patients with PR, baseline DPD level was < 0.1 nmol/min/mg in 4 patients. Five patients had baseline DPD levels ≥ 0.2 nmol/min/mg; SD was the best response in 2 patients (9.8 weeks and 26 weeks) and 3 patients has progressive disease. There was no significant association found between the DPD levels and the responders or patients with SD. Most of the responders (4/5) experienced grade 3 toxicities including leukopenia, dehydration, fatigue, and diarrhea.

Discussion

Based on our prior experience showing efficacy of docetaxel and capecitabine in pretreated NSCLC patients, this phase II two-stage study was designed to evaluate the RR and toxicity

of the combination in treatment-naïve NSCLC. As noted, patients were screened for DPD expression at enrollment. The study was closed after the first stage due to low RR (18% - 5 partial responses) not meeting the criterion for proceeding on to the second stage. No significant trend in response was detected related to DPD expression although most of the patients with partial response had low DPD expression and increased 5-FU related toxicity.

A similar phase II study in Korea also evaluated docetaxel and capecitabine in patients with stage IIIB/IV NSCLC in the first line setting. In this trial, 39 patients were treated with capecitabine 1,000 mg/m² orally twice daily on days 1–14 with docetaxel 36 mg/m² IV on day 1 and 8 of a 21-day cycle. Overall RR was higher (53% with 19 PR (95% CI, 37% to 69%)). The median response duration was 6.2 months (range 2.1–15.7 months). The median OS was 17.8 months with a 1 year survival rate of 56.4% (95% CI, 40.9–72.0%) [23]. Subsequent analysis of TP expression in tumor samples from these patients demonstrated a correlation between RR and TP expression (stromal and tumor). High levels of tumor TP expression with low stromal TP expression was more common in patients with response to chemotherapy ($p = 0.004$ and $p = 0.009$), although there was no significant correlation between TP expression and survival ($p = 0.6$) [24].

There are several limitations of the current study. Although DPD expression was assessed at baseline and day 29, no pharmacokinetic or pharmacogenetic studies were performed to assess dose intensity during therapy. The relative success of fluoropyrimidines in NSCLC in Asian populations suggests that pharmacogenetic differences may exist and account for the higher RRs and perhaps the observed improvement in survival. Particularly in the 5 patients with partial responses, it would have been useful to determine if tumor exposure to 5-FU was significantly increased compared to the rest of the population.

The response was significantly lower than expected. For the trial, patients with significant DPD deficiency were excluded due to concern for toxicity. The trial results suggest, however, that response and toxicity are both likely related to level of drug exposure. Given the important role of enzymatic processes in the activity of fluoropyrimidines, exclusion of DPD deficient patients may adversely impact responses. An alternate approach would be inclusion of DPD deficient patients with titration of dose based on pharmacokinetics, baseline DPD level, and clinical toxicity. If drug exposure within the tumor could be optimized with concurrent docetaxel to modulate TP expression, response may be improved. This would have to be carefully balanced with toxicity related to 5-FU exposure. The experience in this trial suggests that patients with low DPD expression may have enhanced sensitivity to this combination.

The combination of docetaxel and capecitabine in the treatment of chemo-naïve patients with NSCLC in the schedule studied was well tolerated, but did not meet the prospectively set endpoint for response. Results suggest that ongoing evaluation is necessary to optimize the dosing of fluoropyrimidine combinations in this patient population. Given the successful use of fluoropyrimidines in Asian populations, further investigation of pharmacogenetics and novel fluoropyrimidine agents is warranted.

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Figure 1.
Time to progression survival time in days by DPD levels (high vs. low)

Figure 2.
Kaplan-Meier estimate of overall survival in days by DPD level (high vs. low)

Table 1

Patient Characteristics (N=29)

Characteristics	
Patients enrolled	29
Patients evaluable	28
Median Age (Range)	61 (39–76)
Gender	
Male	20
Female	9
Histology	
Adenocarcinoma	13
Squamous cell carcinoma	6
Large Cell Carcinoma	2
NSCLC not otherwise specified (poorly differentiated)	8
Race	
White	25
African-American	4
ECOG performance status	
0	8
1	21

Table 2

Hematologic Toxicity of modulated capecitabine and docetaxel regimen

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	11	3	1	0
Neutropenia	5	4	1	0
Leukopenia	11	6	4	0

Table 3

Non-Hematologic toxicity of modulated capecitabine and docetaxel regimen

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	5	1	0	0
Cardiac – myocardial infarction	0	0	0	1
Fatigue	18	18	5	0
Anorexia	7	10	1	0
Nausea	11	9	2	2
Vomiting	7	7	3	1
Diarrhea	12	8	5	0
Constipation	5	1	0	0
Dehydration	2	3	5	1
Mucositis	15	6	3	2
Dyspnea	6	3	1	0
Hemoptysis	0	0	1	0
Hyperglycemia	2	2	1	0
Hypoglycemia	0	0	1	0
Hypophosphatemia	0	0	1	0
Anxiety/Depression	4	3	0	0
Peripheral neuropathy	7	2	0	0
Skin/nail changes/ hand-foot syndrome	15	9	1	0

Table 4

Overall Response of modulated capecitabine and docetaxel regimen

Response	Number
Patients enrolled	29
Not evaluable	1
Patients evaluable	28
Response Rates (N = 28)	
Complete response (CR)	0
Partial response (PR)	5
Stable disease	14
Disease Progression	9
Overall response (CR + PR)	5
Median Time to Progression	3.3 months
Median Survival	10.5 months