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ORIGINAL ARTICLE

A phase I trial of intermittent high-dose gefitinib and fixed-dose docetaxel in patients with advanced solid tumors

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Abstract
Purpose Based on our mouse xenograft model demonstrating that intermittent high-dose gefitinib sensitizes tumors to subsequent treatment with taxanes, we initiated this phase I trial to explore docetaxel in combination with escalating doses of intermittent gefitinib (Iressa) given prior to docetaxel.
Methods This was a phase I study where patients with advanced cancer were treated with escalating doses of gefitinib (1,000, 1,500, 2,250, 3,000 mg) on days 1 and 2 followed by docetaxel (75 mg/m^2) on day 3 of a 21 day cycle. Gefitinib pharmacokinetic data were obtained on days 1, 2, and 3 of cycles 1 and 2 at each dose level.
Results 18 patients were enrolled in this study with the most frequent tumor types being non-small cell lung cancer and head and neck squamous cell cancer. The dose-limiting toxicity was neutropenia ($n = 1$ at dose level 2, $n = 2$ at dose level 4). Rash, diarrhea, and fatigue were the most common grade 1–2 toxicities. Pharmacokinetic data indicated no accumulation of gefitinib between cycles 1 and 2 and no clear correlation between gefitinib plasma levels and toxicity. Partial responses were observed in one patient with head and neck squamous cell carcinoma and one patient with anaplastic thyroid cancer.
Conclusion The recommended dose for phase II studies is gefitinib 2,250 mg on days 1 and 2, followed by docetaxel 75 mg/m^2 on day 3.

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Introduction

Gefitinib (Iressa[1]) and erlotinib (Tarceva) are epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) of the anilinoquinazoline class [1] and have demonstrated activity in patients with pretreated-non-small cell lung cancer (NSCLC) when administered orally on a daily basis [2]. However, in advanced NSCLC patients, a phase III study with gefitinib (250 mg/day) as second or third line therapy did not show a survival advantage versus placebo [3], whereas a phase III study with erlotinib (150 mg/day) as second or third line therapy did show a survival advantage versus placebo [4]. One possible explanation for the sur-

[1] Iressa is a trademark of the AstraZeneca group of companies.

vival benefit seen with erlotinib (but not with gefitinib) is that erlotinib was administered at the maximum tolerated dose (MTD, 150 mg/day), but gefitinib (250 mg/day) was admininstered below the MTD [5]. In phase III studies of advanced NSCLC patients receiving chemotherapy plus daily EGFR-TKI or placebo, neither erlotinib nor gefitinib when added to chemotherapy as first line treatment showed a survival benefit [6–9].

Based on the above data, one might postulate that daily gefitinib at 250 mg/day suboptimally inhibits EGFR phosphorylation and downstream survival pathways in tumors with wildtype *EGFR* [10]. In support of this hypothesis, pharmacodynamic studies with paired breast tumor biopsies revealed that daily gefitinib therapy failed to inhibit the PI3K/Akt survival pathway [11]. Although similar pharmacodynamic data is not available for NSCLC tumors, the PI3K/Akt pathway mediates resistance to chemotherapy in NSCLC cell lines [12, 13]. These observations suggest that incomplete inhibition of the EGFR tyrosine kinase with daily gefitinib therapy may allow persistent activity of downstream survival pathways in tumors with wildtype *EGFR*, resulting in resistance to chemotherapy. An alternate hypothesis is that tumor stasis induced by daily gefitinib may prevent the chemotherapy from acting on dividing cells.

Intermittent high-dose gefitinib therapy has the potential to overcome these theoretical limitations of daily gefitinib in combination with chemotherapy. Murine xenograft models have compared paclitaxel/gefitinib combinations using both continuous and intermittent schedules of gefitinib administration for several solid tumor types (BT-474 and MX-1 breast cancer, CWR22rv1 prostate cancer, and SK-LC-16 non-small cell lung cancer cell lines) [10]. Intermittent high-dose gefitinib given for 2 days prior to paclitaxel resulted in significantly greater tumor regression and a higher percentage of complete responses in comparison with other schedules. Pretreatment with gefitinib using an intermittent schedule was much more effective than continuous gefitinib in enhancing the antitumor activity of paclitaxel, both in cell lines that are sensitive (BT-474 and MX-1) and resistant (CWR22rv1 and SK-LC-16) to gefitinib monotherapy [10]. As such, intermittent pulsing of gefitinib prior to taxane chemotherapy may have utility against tumors that are resistant to conventional dosing of gefitinib.

Phosphorylated Akt levels in tumors were decreased by intermittent gefitinib in the preclinical model, suggesting that this treatment may sensitize cells to apoptosis by inhibiting the PI3K/Akt survival pathway [14]. None of the tumors harbored *EGFR* kinase domain mutations, which are associated with response to conventional gefitinib dosing [15]. The clinical implication is that pulse administration of gefitinib may enhance clinical responses to chemotherapy in tumors that harbor wildtype *EGFR*.

Chronic daily dosing of gefitinib or erlotinib is limited by toxicities that include rash and diarrhea. Intermittent administration of EGFR-TKI allows us to escalate the dose higher than the MTD with daily administration. We previously conducted a study with single agent once weekly erlotinib and were able to administer 2,000 mg of erlotinib once weekly without dose-limiting toxicity [16]. This phase I trial explores intermittent high dose gefitinib given for 2 days prior to docetaxel on a 21-day schedule. Based on our data with weekly single agent erlotinib, we decided upon a conservative starting dose of gefitinib of 1,000 mg days 1 and 2 followed by day 3 docetaxel every 3 weeks. The study was designed to determine the pharmacokinetics, safety and tolerability of this treatment, and to establish a recommended dose for phase II studies.

Patients and methods

Patient selection

Patients had an advanced solid tumor refractory to standard treatment or for which there was no standard treatment. Evaluable or measurable indicator lesions were required. No more than two prior chemotherapy regimens for metastatic cancer were permitted. A minimum of 3 weeks must have elapsed since last chemotherapy or radiation therapy to major bone-marrow containing area. Karnofsky Performance Status $\geq 70\%$, WBC $\geq 3{,}000$ per μl, hemoglobin ≥ 9.0 g/dl, platelet count $\geq 100{,}000/\mu l$, serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 55 ml/min, total bilirubin $\leq 1.5 \times$ upper limit of normal (UNL) (≤ 1.5 mg/dl), and AST $\leq 2.0 \times$ UNL (≤ 74 U/l) were required. After the fourth patient, the trial was amended to require baseline values within normal limits for total bilirubin (0–1.0 mg/dl), AST (10–37 U/l), and ALT (5–37 U/l). Patients who were dependent on percutaneous gastrostomy tube for administration of gefitinib tablets were not excluded. Patients with prior treatment with docetaxel, gefitinib, or erlotinib were excluded. Patients were excluded if they required co-administration of antacids, H-2 blockers, proton pump inhibitors, warfarin, or potent inhibitors/inducers of CYP3A4. Due to preclinical data indicating that high doses of gefitinib may lead to prolongation of the QT_c interval, after October 2004 patients were excluded for congenital long QT syndrome, QT_c interval ≥ 450 ms on baseline

electrocardiogram, bradycardia, history of torsades de pointes, pre-existing conditions known to be causally associated with prolonged QT_c interval, or use of medications known to prolong QT_c (listed under Drug List 1 by the Arizona Center for Education and Research on Therapeutics, reference web page http://www.torsades.org). The study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board (IRB). All patients provided written informed consent.

Baseline evaluation

Pretreatment evaluation included: complete history and physical; laboratory evaluation including complete blood count and comprehensive serum chemistries; baseline electrocardiogram; and appropriate CT scanning of relevant disease sites within 4 weeks of study entry.

Dose limiting toxicity (DLT)

Toxicity was assessed according to NCI common toxicity criteria (CTC) version 3.0. DLT was defined as any of the following toxicities occurring during the first cycle of therapy: grade 4 neutropenia (ANC < 500 per mm^3) for more than 7 days; grade 4 neutropenia accompanied by fever; grade 4 thrombocytopenia; any grade 3 hematologic toxicity requiring treatment delay beyond 2 weeks; grade 3 diarrhea lasting longer than 48 h or grade 4 diarrhea; rash ≥ grade 3 or requiring dose delay ≥ 2 weeks; grade 3 fatigue lasting ≥ 1 week; other non-hematologic treatment-related grade 3 or 4 toxicities. After October 2004, QT_c prolongation > 550 ms was added to the definition of DLT.

Dose escalation and definition of maximum tolerated dose

The starting dose of gefitinib was 1,000 mg on days 1 and 2 of each cycle. The gefitinib dose escalation scheme is shown in Table 1. The gefitinib-starting dose was selected empirically, largely based on our prior experience with intermittently pulsed erlotinib in a phase I/II study [16]. Three patients were enrolled at the first dose level; if no DLT was observed, three patients were enrolled at the next dose level. If one DLT was observed, the dose level was expanded to six patients. If two DLTs were observed, the maximum tolerated dose (MTD) was exceeded and the dose level below was expanded to a total of six patients, and if ≤ 1 out of six patients experienced a DLT at this dose level, this would be the recommended phase II dose. Completion of one cycle of therapy (3 weeks) by all patients at any dose level was required before any patients could be enrolled at the next dose level. There was no intrapatient dose escalation.

Treatment plan

Patients received oral gefitinib on days 1 and 2, followed by docetaxel 75 mg/m^2 intravenously over 1 h on day 3 every 3 weeks. Gefitinib tablets (250 mg) were administered on days 1 and 2. Dexamethasone (8 mg per oral twice daily for three days starting 12 h prior to each docetaxel infusion) was administered. In the absence of progressive disease or unacceptable toxicity, patients were permitted to receive docetaxel and gefitinib indefinitely; monotherapy with gefitinib or docetaxel was not permitted. Treatment response was assessed using RECIST criteria, June 1999 revised version [17].

Toxicity assessment and dose modifications

Patients were examined and toxicities were graded on days 1, 8, and 15 of cycle 1 and on day 1 of subsequent cycles. For patients experiencing grade 3 or 4 diarrhea, gefitinib was discontinued for a maximum of 14 days. If diarrhea resolved to ≤ grade 1 within 14 days, gefitinib was restarted with a 25% dose reduction.

When the study opened, pretreatment surface electrocardiograms were obtained on days 1 and 2 of cycles 1 and 2. After 2004, more intensive monitoring of the QT_c interval was instituted due to preclinical data indicating that high doses of gefitinib may lead to

Table 1 Exposure to gefitinib and docetaxel

Dose level	Gefitinib (mg, days 1 and 2)	Docetaxel (mg/m^2, day 3 every 21 days)	No. of patients treated	Median no. of cycles (range)	No. of patients with docetaxel dose reductions
1	1,000	75	3	8 (2–14)	1
2	1,500	75	6	4.5 (2–8)	2
3	2,250	75	6	4.5 (1–16)	0
4	3,000	75	3	2 (1–10)	1

prolongation of the QT_c interval. Pretreatment surface electrocardiograms were obtained on days 1–3, and a 5-h post-treatment electrocardiogram was obtained on day 1 of cycle 1.

For all other non-hematologic grade 3 toxicities excluding nausea/vomiting, treatment was withheld and patient was reassessed in 1 week. If toxicity resolved to ≤ grade 2 or less in 1 week, treatment was resumed with 25% dose reductions in both gefitinib and docetaxel. Patients were removed from study for all other non-hematologic grade 4 toxicities.

Hematologic parameters were measured on day 1 of each cycle. Patients developing grade 4 neutropenia lasting ≥ 7 days, febrile neutropenia, or thrombocytopenia (platelets < 100,000 per μl) had docetaxel held until recovery of blood counts to ≤ grade 1. Once counts recovered, docetaxel was resumed with 25% dose reduction. Patients were taken off study if blood counts failed to resolve to grade 1 or better after a maximum of 3 weeks.

For treatment delays other than those outlined in the toxicity management guidelines above, the protocol mandated that patients be removed if treatment was delayed for more than 1 week.

Pharmacokinetics

All patients provided venous blood for the determination of plasma concentrations of gefitinib before treatment on days 1, 2, and 3 of cycle 1 and 2 only. Venous blood (4 ml) was collected into tubes containing lithium heparin anticoagulant. Within 60 min of collection, blood samples were centrifuged at $1{,}000 \times g$ for 10 min. Plasma supernatant was stored at −20°C. Pharmacokinetic analysis by high performance liquid chromatography and tandem mass spectrometry was performed at Analytico Medinet (Breda, The Netherlands).

Results

Patient characteristics

Eighteen patients with advanced solid tumors were accrued between May 28, 2004 and May 4, 2005. Patient characteristics are outlined in Table 2. The median age was 60 years, and 12 patients were men. Patients received a median of 1 prior chemotherapy regimen; the numbers of prior chemotherapy regimens were 2 ($n = 4$ patients), 1 ($n = 10$ patients), and 0 ($n = 4$ patients). The tumor types represented in this trial were non-small cell lung cancer ($n = 8$ patients), head and neck squamous cell carcinoma ($n = 7$), anaplastic thyroid cancer ($n = 1$), nasopharynx cancer ($n = 1$), and adenoid cystic carcinoma ($n = 1$).

Table 2 Patient characteristics

No. of patients	18
Median age (year)	60 (range 39–77)
Women	6
Men	12
Number prior chemotherapies, median	1 (range 0–2)
Number prior radiation therapies, median	1 (range 0–3)
Karnofsky performance status, median (%)	80 (range 70–90)
Tumor types	
Non-small cell lung cancer	8
Head and neck squamous cell cancer	7
Nasopharynx cancer	1
Anaplastic thyroid cancer	1
Adenoid cystic carcinoma	1

Adverse events

All 18 patients enrolled received at least one cycle of treatment. The median number of cycles completed per patient was 4.5 (range 1–16). Table 3 summarizes adverse events during cycle 1 which were considered possibly related to treatment. At the first dose level (gefitinib 1,000 mg on days 1 and 2), no dose-limiting toxicities occurred. Two patients experienced grade 3–4 neutropenia. All patients at this dose level developed grade 1–2 rash during cycle 1.

For the first patient at the second dose level (1,500 mg on days 1 and 2), baseline bilirubin was 1.4 mg/dl (normal ≤ 1.0 mg/dl). During cycle 1, he experienced dose limiting febrile neutropenia, grade 3 hyperbilirubinemia, and grade 2 rash. The protocol was subsequently amended to exclude patients with any baseline abnormalities in liver function tests, and this dose level was expanded to six total patients with no further dose-limiting toxicity. Among six patients at this dose level, five developed grade 1–2 rash.

At the third dose level (gefitinib 2,250 mg on days 1 and 2), no DLTs were observed. During cycle 1, one patient experienced left lower extremity cellulitis without significant neutropenia, resulting in treatment delay of greater than one week. Although the cellulitis was deemed unrelated to study treatment, the protocol mandated removal of the patient from study due to treatment delay. Subsequently, three patients were enrolled at dose level 4 (gefitinib 3,000 mg on days 1 and 2).

At dose level 4 (3,000 mg on days 1 and 2), two of three patients experienced dose limiting toxicities and

Table 3 Toxicities at each dose level during cycle 1

Dose Level (n = no. of patients)	1 (n = 3)				2 (n = 6)				3 (n = 6)				4 (n = 3)				
Gefitinib dose (days 1 and 2)	1,000 mg				1,500 mg				2,250 mg				3,000 mg				
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	5
Neutropenia			1	1		1	1	1		1	1					1	1
Anemia	1				1						1		1	1			
Thrombocytopenia					1											1	
Rash	2	1			2	3			5					2			
Diarrhea	1				1				3								
Fatigue	2				2	3			4				1				
Stomatitis					1				1				1				
Hyperbilirubinemia	1					1	1		3								
ALT elevation	1				1				1				1				
AST elevation					1				1								
Creatinine elevation														1			

the MTD was exceeded; one patient had grade 4 neutropenia lasting more than 7 days and the second patient experienced febrile neutropenia that ultimately led to her death. This grade 5 toxicity occurred in a 47-year-old woman with stage IV NSCLC who had received one prior chemotherapy regimen as well as radiation. On day 9 of cycle 1, she was admitted to an outside hospital with neutropenic fever. Liver function tests were normal. She was treated with intravenous antibiotics. Neutropenia resolved by hospital day 4, but she developed worsening respiratory distress and increasing white blood cell count attributed to progressive pneumonia. The patient died on hospital day 11. Laboratory abnormalities in the two final days of her life (including grade 4 thrombocytopenia, grade 2 anemia, grade 2 creatinine elevation, and grade 1 AST elevation) were felt to represent sepsis with multiorgan failure, and are included in Table 3.

Because the MTD was exceeded at the fourth dose level, the dose level below (dose level 3) was expanded to six total patients. No DLTs were observed at dose level 3.

Table 4 summarizes cumulative toxicities (all cycles) which were considered possibly related to treatment; adverse events are shown if at least one patient experienced $\geq$ grade 3 toxicity and/or $\geq$ 25% of patients experienced grade 1 or 2 toxicity. Grade 1–2 transient rash was the most common toxicity, occurring in 15/18 (83%) patients, but there were no cases of dose limiting rash. Among eight patients who remained on study for six or more cycles, grade 1–2 rash recurred with most, but not all, subsequent treatment cycles. Diarrhea was mild and not dose limiting in this study; 10/18 (55%) patients experienced grade 1 diarrhea and 3/18 (17%) patients experienced grade 2 diarrhea. Additional non-hematologic toxicities included grade 1 or 2 fatigue in 13/18 (72%) patients, grade 1 nausea in 6/18 (33%) patients, grade 1 or 2 hyperbilirubinemia in 5/18 (28%), grade 1 stomatitis in 4/18 (22%), and grade 1 or 2 nail changes in 4/18 (22%) patients. None of the non-hematologic toxicities demonstrated obvious worsening associated with escalation of gefitinib through dose levels 1–4. Cardiac monitoring with serial electrocar-

Table 4 Cumulative toxicities at each dose level (all cycles)

Dose level (n = no. of patients)	1 (n = 3)				2 (n = 6)				3 (n = 6)				4 (n = 3)				
Gefitinib dose (days 1 and 2)	1,000 mg				1,500 mg				2,250 mg				3,000 mg				
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	5
Neutropenia			1	1		1	2	1		1	2				2	1	1
Anemia	1				1				1		2		1	1			
Thrombocytopenia					1											1	
Rash	2	1			2	3			5					2			
Diarrhea	3				3				3	2			1	1			
Nausea	1				2				2				1				
Neuropathy (sensory)	1								3	1			2				
Edema	1				1		1		1								
Hyperbilirubinemia	1					1	1		3								

diograms did not reveal clinically significant QT_c prolongation at any dose level.

Pharmacokinetics

Gefitinib plasma concentrations were determined for all 18 patients on study prior to treatment on days 1, 2 and 3 of the first 2 cycles. The cycle 1, day 1 pre-dose samples had no quantifiable levels of gefitinib (limit of quantification 0.5 ng/ml), with the exception of two patients who had small but detectable levels of gefitinib (1.20 and 0.608 ng/ml).

At each dose level, there was marked variability of gefitinib plasma concentrations between patients, as evidenced by the standard deviations in Fig. 1. The overall mean pre-dose levels for day 2 and day 3 increased with dose from 1,000 mg to 2,250 mg, but there appeared to be no further increase achieved for the 3,000 mg dose level (Fig. 1). The pre-dose levels (mean and standard deviation) on day 3 were 520 ± 147 ng/ml (1.2 ± 0.3 μM) at dose level 1; 803 ± 255 ng/ml (1.8 ± 0.6 μM) at dose level 2; $1{,}771 \pm 900$ ng/ml (4.0 ± 2.0 μM) at dose level 3; and $1{,}834 \pm 295$ ng/ml (4.1 ± 0.7 μM) at dose level 4. With two exceptions, the day 2 pre-dose value was less than that on day 3 (data not shown). For one patient at dose level 3, the pre-dose cycle 2 day 3 concentration was 48.5 ng/ml, compared to that on day 2 of 651 ng/ml and of 562 and 890 ng/ml for cycle 1 pre-dose days 2 and 3, respectively. The value was not used in the determination of the mean concentration on that day for the 2,250 mg dose level.

There was no evidence of accumulation of gefitinib between cycles (compare Fig. 1a, b). With two exceptions, by day 1 of cycle 2, the gefitinib plasma concentration was less than 1% that of the concentration on day 3 of cycle 1 (data not shown).

We explored whether there was a relationship between toxicities and gefitinib plasma concentrations in cycle 1. At dose level 2, one patient experienced dose-limiting febrile neutropenia in cycle 1. The gefitinib concentration prior to treatment on day 3 was 961 ng/ml, compared with 662 ± 145.7 ng/ml for patients who did not experience DLT ($n = 5$). For the patient at dose level 4 who suffered fatal febrile neutropenia during cycle 1, the plasma gefitinib concentration prior to treatment on day 2 was 2,600 ng/ml, which was the highest plasma gefitinib concentration of any patient in the study during cycle 1. However, in a comparison of all patients who experienced neutropenia ≥ grade 2 with patients who did not experience neutropenia during cycle 1, gefitinib plasma concentrations prior to treatment on day 3 of cycle 1 were similar for both groups of patients (mean $1{,}289 \pm 708$ ng/ml for nine patients without neutropenia, versus $1{,}116 \pm 596$ ng/ml for nine patients with neutropenia ≥ grade 2).

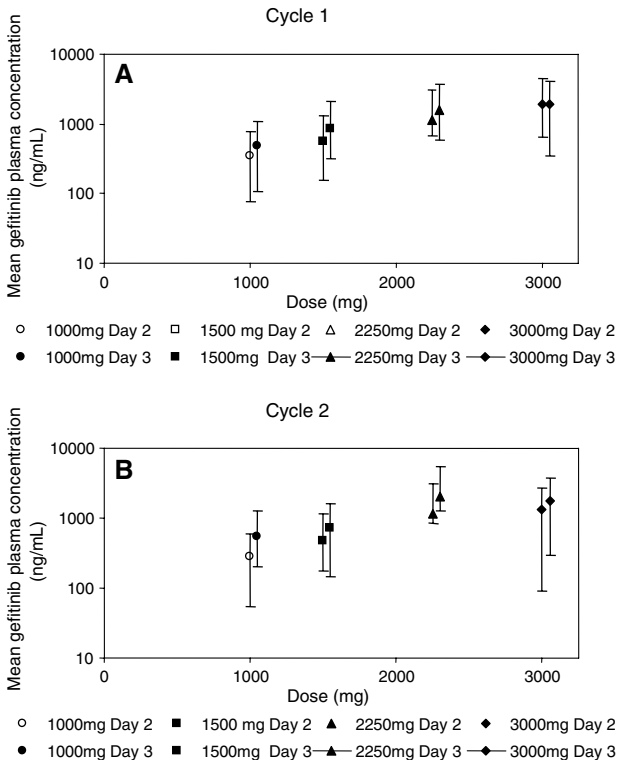

Fig. 1 Overall mean pre-dose plasma gefitinib concentrations with standard deviations at each dose level on days 2 and 3 for cycle 1 (**a**) and cycle 2 (**b**). Standard deviations are indicated by *error bars*

Efficacy

Objective radiologic response was assessed for all 18 patients. There were 2 objective partial responses. At dose level 3, an objective radiologic partial response was observed in a 61-year-old man with oropharynx squamous cell carcinoma metastatic to lung who had received 1 prior chemotherapy regimen, but he withdrew consent for study participation after 3 cycles. A 50-year-old man with anaplastic thyroid cancer metastatic to skin was treated at dose level 2 after having received 1 prior chemotherapy regimen; he experienced significant partial reduction of multiple dermal nodules for approximately 4 months before coming off study due to pulmonary embolism. One patient with recurrent nasopharyngeal carcinoma involving skull base had near-resolution of headache pain for approximately 5 months, although he had stable disease by CT scan. For eight patients with stable disease, the diagno-

Table 5 Best response and duration of therapy

Dose level	No.of priors	No. of cycles	Best response
NSCLC patients			
2	1	2	POD
2	2	2	SD
2	0	4	SD
2	0	6	SD
3	0	6	SD
3	2	16	SD
4	1	1	NE
4	1	2	POD

Dose level	Diagnosis	No. of priors	No. of cycles	Best response
B Head and neck cancer patients				
1	HNSCC/oropharynx	2	2	POD
1	HNSCC/oropharynx	1	14	SD
1	HNSCC/hypopharynx	1	8	SD
2	Nasopharynx cancer	2	8	SD
2	Anaplastic thyroid	1	5	PR
3	HNSCC/oral cavity	1	2	POD
3	HNSCC/oropharynx	1	3	PR
3	Adenoid cystic carcinoma	0	1	NE
3	HNSCC/oropharynx	1	6	SD
4	HNSCC/oropharynx	1	10	SD

POD progression of disease, *SD* stable disease, *NE* not evaluable, *PR* partial response

ses were HNSCC (6, 8, 10, and 14 cycles), NSCLC (6, 6, and 16 cycles), and nasopharyngeal carcinoma (8 cycles). As such 10 of 18 patients (56%) experienced either partial response or stable disease for at least 6 cycles. Table 5 shows best response and duration of therapy for patients with (A) NSCLC and (B) head and neck cancers.

Therapy was discontinued due to progression of disease in 11 patients. Three patients were removed from study due to cumulative grade 1–2 toxicities (fatigue, rash, diarrhea, neuropathy, nausea and vomiting) after 6, 6, and 10 cycles, respectively. Other reasons for study discontinuation in one patient each were: patient withdrawal, patient noncompliance after 14 cycles, pulmonary embolism after 5 cycles, and treatment delay due to cellulitis after 1 cycle.

Discussion

This study demonstrates that high-dose gefitinib given for 2 days prior to docetaxel chemotherapy is feasible in patients with advanced solid tumors. The dose-limiting toxicity was neutropenia, and the most common toxicity was rash. The recommended phase II dose is gefitinib 2,250 mg orally on days 1 and 2 followed by docetaxel 75 mg/m^2 intravenously on day 3 of a 21-day cycle.

High-dose gefitinib administered prior to docetaxel was well tolerated in most patients. Both drugs, particularly gefitinib, have been associated with rash. Studies of daily gefitinib therapy have observed anecdotally that rash often resolves after several cycles of continuous gefitinib [18]. In this study of intermittent high-dose gefitinib, rash tended to recur.

Neutropenia is well established as the dose-limiting toxicity of docetaxel and although our MTD was exceeded due to neutropenia, it is not clear whether this represents an enhanced toxicity with the addition of gefitinib or rather an expected occurrence with docetaxel 75 mg/m^2 dosing. Grade 3 or higher neutropenia was observed in 9/18 (50%) patients during the course of the study, which is consistent with previous publications with docetaxel as second or third line therapy [19, 20]. In the current study, 7/18 (39%) of patients experienced ≥ grade 3 neutropenia during first cycle of therapy. In particular, two of three patients at dose level 4 experienced grade 4 or grade 5 neutropenia with the first cycle of treatment, suggesting there may be enhanced neutropenia with this regimen at the higher dose levels. High intermittent doses of gefitinib alone are unlikely to cause neutropenia, as no significant neutropenia was observed in a phase I dose escalation study of weekly erlotinib [16]. Additionally, daily gefitinib therapy at standard doses (250 or 500 mg/day) does not appear to alter docetaxel exposure for most patients [21]. Therefore, if enhanced neutropenia was observed with this combination, it appears unique to this schedule of administration.

In support of the hypothesis that the toxicity of docetaxel may have been increased by high doses of gefitinib in some patients, both drugs are extensively metabolized by cytochrome P450 CYP3A4 enzyme [22–25]. This enzyme demonstrates wide variation in expression and activity between individuals [26]. As such, individuals with low CYP3A4 activity may experience profound inhibition of docetaxel clearance in the setting of high-dose gefitinib therapy. This process could enhance docetaxel-related neutropenia in these patients. However, only gefitinib, but not docetaxel pharmacokinetics were obtained as part of this study.

Pharmacokinetic analysis is limited by the sample size and the considerable overlap of gefitinib levels between individual patients at different dose levels (i.e. between 1,000 and 1,500 mg, 1,500 and 2,250 mg, and 2,250 and 3,000 mg). The data here demonstrates that mean plasma levels of gefitinib increased with dose over the dose range 1,000–2,250 mg, but there is an apparent saturation effect on absorption of these high

doses based on the comparison of mean plasma levels after 2,250 and 3,000 mg, respectively. Given this apparent plateau in bioavailability with oral administration, development of intravenous EGFR-TKIs for high dose pulsing regimens may be of interest.

At the phase II recommended dose (gefitinib 2,250 mg on days 1 and 2), the cycle 1 day 3 mean pre-dose plasma concentration of gefitinib was 4.0 μM. The mean maximum plasma concentration (C_{max}) of conventional daily dosing of gefitinib (250 mg/day) is approximately 159 ng/ml, or 0.36 μM [27]. It is not known if the increased C_{max} may improve anti-tumor efficacy.

Previous studies have shown that after a single dose of gefitinib, plasma concentrations decline from the C_{max} with a biphasic disposition. Assuming the second phase of this biphasic disposition starts about 24 h after dosing, a linear extrapolation from the cycle 1 day 3 pre-dose concentration to the cycle 2 day 1 pre-dose concentration demonstrates that the 1,000 mg regimen maintains a plasma concentration of gefitinib that is above the mean steady state value achieved with once daily dosing at 250 mg for a median time of 5 days, 1,500 mg a median time of 7 days, and 2,250 mg a median time of 10 days. There were only two patients with such data at 3,000 mg, where levels were maintained for 8 and 15 days.

There were two partial responses, one in HNSCC and one in anaplastic thyroid cancer. Preclinical and clinical data indicates that EGFR signaling appears to be important in the tumor biology of at least some HNSCC and anaplastic thyroid cancers, supporting the further development of EGFR-directed therapies in these patient populations [28, 29]. Eight patients demonstrated stable disease for at least six cycles of treatment. Efficacy was not an endpoint in this phase I study, and future studies will be needed to determine if this treatment regimen is superior to either docetaxel or gefitinib alone in any solid tumor patients.

Another phase I trial evaluated docetaxel and intermittently pulsed erlotinib on a different schedule. Docetaxel was given on day 1, and erlotinib was given on days 2, 9, and 16 of a 21-day cycle. The maximum tolerated dose was reached at docetaxel 70 mg/m^2 and weekly erlotinib 600 mg [30]. From preclinical models, it is not clear if the sequence of administration of EGFR-TKI and taxane is an important determinant of cytotoxicity. In studies of NSCLC cell lines in vitro, two groups found that induction of apoptosis occurred more efficiently with the sequence of taxane followed by erlotinib, compared to the reverse schedule [31–33]. In contrast, data from our xenograft model suggests that inhibition of cancer cell survival pathways best occurs when gefitinib is given before taxanes [14]. The optimal sequence of pulse gefitinib and chemotherapy may be influenced by the sensitivity of the tumor to gefitinib as a single agent, but this possibility has not been addressed directly in the preclinical studies.

This phase I trial demonstrates the feasibility of the administration of pulse gefitinib given prior to chemotherapy as a clinical research paradigm. The recommended phase II dose for this experimental regimen is gefitinib 2,250 mg orally on days 1 and 2, followed by docetaxel 75 mg/m^2 intravenously on day 3 of a 21-day schedule. To fully investigate this approach, preclinical and phase I studies should evaluate combinations of other cytotoxic drugs and pulsed small molecule kinase inhibitors. Ideally, the cytotoxic agent and the kinase inhibitor should have non-overlapping catabolic pathways to minimize potential toxicities.

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