**Phase I, Pharmacokinetic, and Biological Study of Erlotinib in Combination with Paclitaxel and Carboplatin in Patients with Advanced Solid Tumors**

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**Abstract**

**Purpose:** To assess the feasibility of administering erlotinib, an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase, in combination with paclitaxel and carboplatin, and to identify pharmacokinetic interactions, evaluate downstream effects of EGFR inhibition on surrogate tissues, and seek preliminary evidence for clinical activity.

**Experimental Design:** Patients with advanced solid malignancies were treated continuously with erlotinib at doses of 100, 125, and 150 mg/d orally along with fixed i.v. doses of paclitaxel 225 mg/m² and carboplatin AUC 6 mg-min/mL, both on day 1 every 3 weeks.

**Results:** Twenty evaluable patients were treated with 136 courses of erlotinib, paclitaxel, and carboplatin. Myelosuppression, skin rash, and diarrhea were the principal toxicities. Dose-limiting diarrhea occurred in 1 of 6 patients at the 100 mg erlotinib dose level, whereas 0 of 9 evaluable patients at the 125 mg erlotinib dose level experienced dose-limiting toxicity and 3 of 5 evaluable patients at 150 mg erlotinib experienced dose-limiting skin rash and neutropenic sepsis. There was no evidence of pharmacokinetic interactions between paclitaxel and erlotinib; however, total carboplatin exposure trended higher in the presence of erlotinib. No consistent downstream effects on EGFR inhibition were found in skin. Durable objective responses were observed in non–small-cell lung and head and neck cancers.

**Conclusions:** A dose level of erlotinib 125 mg combined with paclitaxel 225 mg/m² and carboplatin AUC 6 mg-min/mL is recommended for disease-directed studies. This phase I trial was followed by a randomized phase III study in non–small-cell lung cancer using a similar regimen.

The epidermal growth factor receptor (EGFR; ErbB1), a 170-kDa plasma membrane glycoprotein, is a member of the tyrosine kinase receptor family of four closely related receptors: EGFR (ErbB-1), Her2/neu (ErbB-2), Her3 (ErbB-3), and Her4 (ErbB-4; refs. 1, 2). A vast array of human solid tumors, including breast, non–small cell lung (NSCLC), ovarian, colorectal, and head and neck cancers, express EGFR, which is also linked to malignant transformation (3–6). Furthermore, EGFR gene amplification and rearrangements are frequently found in gliomas, whereas activating mutations within the tyrosine kinase domain have now been well described in patients with NSCLC (7–10). Given the importance of EGFR in tumorigenesis, its association with poor prognosis, as well as response to therapy, it is clearly a rational target for therapeutic inhibition (3, 5, 11, 12).

To date, the two major strategies for abrogating EGFR function have been the use of monoclonal antibodies directed against the extracellular domain of the receptor and the use of quinazolinamine-based small molecules that compete for the ATP-binding site within the EGFR tyrosine kinase domain. Both approaches ultimately result in impairment of the catalytic activity of the receptor and its ability to induce downstream signals (13, 14). The small-molecule tyrosine kinase inhibitors have differential specificities towards various receptors in the HER family, with the capacity to block one or more members. Erlotinib hydrochloride (erlotinib, OSI-774; Tarceva, OSI Pharmaceuticals, Inc., Melville, New York), a quinazolinamine derivative, is an orally available reversible and selective inhibitor of EGFR tyrosine kinase with an IC50 of 2 nmol/L (0.79 ng/mL).
The rationale for evaluating the administration of erlotinib in combination with paclitaxel and carboplatin includes the established role of paclitaxel and carboplatin in NSCLC and ovarian cancer, the distinct spectrum of anticancer activity shown with erlotinib in multiple solid tumors (NSCLC, ovary, head and neck), and the widely disparate mechanisms of action of these agents. This study was also designed to provide the toxicologic and pharmacologic foundation for disease-directed trials. The objectives of this study were to (a) characterize the principal toxicities of erlotinib administered once daily in combination with fixed doses of paclitaxel (225 mg/m² i.v. every 3 weeks) and carboplatin (AUC 6 mg-min/ml every 3 weeks i.v.) in patients with advanced solid malignancies; (b) determine the maximum tolerated dose of erlotinib in combination with paclitaxel and carboplatin on this dose schedule and recommend doses for subsequent disease-directed trials; (c) describe the pharmacokinetics of erlotinib, paclitaxel, and carboplatin in combination and determine if there are major effects of erlotinib on the clearance of paclitaxel and carboplatin; (d) seek preliminary evidence of antitumor activity in patients with advanced malignancies; and (e) determine whether changes in downstream signaling proteins are detectible in surrogate tissue.

Materials and Methods

Patients with histologically confirmed advanced solid malignancies refractory to standard therapy or for whom no effective therapy existed were candidates for this study. Eligibility criteria included (a) age of ≥18 years; (b) Eastern Cooperative Oncology Group performance status ≤2 (ambulatory and capable of self-care); (c) no chemotherapy, radiotherapy, or investigational therapy within the previous 4 weeks (6 weeks for nitrosoureas or mitomycin C); (d) adequate hematopoietic (absolute neutrophil count ≥1,500/µL, platelets ≥100,000/µL, and hemoglobin ≥9 g/dL), hepatic (total bilirubin ≤1.5 times the institutional normal limits, aspartate aminotransferase and alanine aminotransferase <3.0 times the institutional upper normal limits, unless due to hepatic metastases, in which case elevations of <5.0 times the upper normal limits were permitted), and renal (serum creatinine <1.5 times the institutional upper normal limits, or a calculated creatinine clearance of ≥60 mL/min according to the modified Cockroft and Gault formula) functions; (e) no prior extensive myelotoxic therapy [defined as ≥6 courses of alkylating agent–containing chemotherapy (except low-dose cisplatin), mitomycin C or a nitrosourea, irradiation to ≥25% of hematopoietic reserves]; (f) no prior exposure to full doses of paclitaxel or carboplatin; (g) no prior exposure to EGFR targeting agents; (h) no concurrent radiation therapy, chemotherapy, hormonal therapy, or immunotherapy; (i) no significant ophthalmologic conditions (including keratoconjunctivitis sicca, Sjogren’s syndrome, or disorders that might increase the risk for epithelium-related complications); and (j) no coexisting medical conditions likely to interfere with study procedures. Written informed consent was obtained according to federal and institutional guidelines.

Dosage and dose escalation

The starting dose of erlotinib was 100 mg orally daily (qd) from day 3 of the first course without interruption. The dose of erlotinib was escalated to 150 mg qd with the option to evaluate an intervening dose of 125 mg qd to more fully characterize the toxicities. The dose of paclitaxel was fixed at 225 mg/m² i.v., administered on day 1 and repeated every 21 days. The dose of carboplatin was targeted to a fixed area under concentration-time curve of 6 mg-min/ml, administered on day 1 and repeated every 3 weeks. A course was defined as 3 weeks in length. Chemotherapy was continued, according to the disease type, for a standard number of cycles and thereafter patients were maintained on erlotinib until disease progression or drug intolerance. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). A minimum of three new patients were treated at the first dose level of erlotinib. If dose limiting toxicity (DLT) was not observed in the first three patients, then the dose of erlotinib was increased to the next level. If DLT occurred in any of the first three new patients in the first course, at least three additional new patients were treated. If no more than one further DLT was encountered, dose escalation proceeded. Alternately, if DLT was noted in two or more of three additional subjects, dose escalation was to be terminated and the maximum tolerated dose was defined as the highest dose level at which one third of at least six new patients experienced DLT in course 1. During the conduct of this trial, there was an option to evaluate an intervening dose of erlotinib (125 mg qd). Intrapatient dose escalation was not permitted. The following events were considered dose limiting if attributable to erlotinib exposure: (a) absolute neutrophil count <500/µL for longer than 5 days or an absolute neutrophil count <1,000/µL associated with fever (temperature ≥38°C) or infection requiring parenteral antibiotics; (b) platelet count <25,000/µL; (c) any drug-related grade 3 or 4 nonhematologic toxicity, except alopecia, grade 3 self-limiting fatigue, grade 3 tolerable rash, or diarrhea, nausea, and vomiting in the absence of optimal supportive medication; (d) inability to complete one 3-week course of therapy due to toxicity; (e) treatment delay >7 days due to unresolved toxicity.

Dose reductions of paclitaxel and/or carboplatin were done in patients with DLT. The dose of either or both agents was reduced, as clinically indicated, to 175 mg/m² and AUC 5 mg-min/ml for paclitaxel and carboplatin, respectively. Patients who experienced either clinically intolerable or dose limiting skin rash and/or diarrhea received a maximum of two dose reductions of erlotinib. The dose of erlotinib was reduced from the 150 and 125 mg dose levels to 100 mg followed by 75 mg daily, whereas those patients commencing at a dose of 100 mg daily were reduced to 75 mg followed by 50 mg daily as indicated for toxicities.

Drug administration

Erlotinib hydrochloride, supplied by OSI Pharmaceuticals as 150, 100, and/or 25 mg tablets as the free base, was administered daily on a continuous schedule. Paclitaxel was obtained commercially as a 6 mg/ml solution and carboplatin was obtained commercially as a 1 mg/ml solution. Both agents were diluted with 250 mL of normal saline before administration. All patients received diphenhydramine (50 mg) and an H2 receptor antagonist administered i.v. 30 min before the paclitaxel infusion and dexamethasone (20 mg) orally 12 and 6 h before paclitaxel. Patients received paclitaxel as a 3-h infusion diluted in 500 mL of sterile and isotonic (0.9%, v/v) sodium chloride solution (saline). After completion of the paclitaxel infusion, 100 mL of saline were infused over 30 min, followed by an infusion of ondansetron (8 mg) or equivalent serotonin 5-HT3 receptor antagonist diluted in 100-mL saline given over 30 min. Thereafter, the total calculated dose of carboplatin, diluted in 500 mL of 5% (weight/volume) dextrose solution, was administered over 30 min.

Pretreatment assessment and follow-up studies

History, physical examination, and routine laboratory studies were done pretreatment and at least weekly during the first two courses, and then before each new course. Routine laboratory studies included serum electrolytes, chemistries, renal and liver function tests, complete blood cell and differential WBC counts, coagulation studies, and urinalysis. Ophthalmologic evaluations, which included an ophthalmic
mixed with an internal standard and water and extracted into spectrometry methods. Briefly, aliquots of the thawed samples were the metabolite OSI-420 by liquid chromatography-tandem mass for determination of erlotinib and OSI-420 (principal metabolite) concentrations were obtained pretreatment, 15, 30, and 60 min and 2, 4, 6, and 8 h after dosing, and on days 8 and 15 before dosing. During course 2, plasma samples for erlotinib were obtained pretreatment, 15, 30, and 60 min and 2, 4, 6, and 8 h after dosing, as well as on days 2, 3, 8, and 15 before dosing. For each sample, at least 2 mL of whole blood were collected in heparinized tubes (carboplatin and erlotinib) or K-EDTA tubes (paclitaxel), kept on ice, and centrifuged within 1 h at 2,000 × g for 10 min to isolate plasma. Plasma was frozen immediately in cryogenic tubes and stored at ≤−20°C for later analysis.

Plasma samples were analyzed for concentrations of erlotinib and the metabolite OSI-420 by liquid chromatography-tandem mass spectrometry methods. Briefly, aliquots of the thawed samples were mixed with an internal standard and water and extracted into t-butyl methyl ether. The organic layer was evaporated to dryness under nitrogen and the residue reconstituted in mobile phase for analysis. Separation of analytes was accomplished by reverse-phase high-performance liquid chromatography followed by mass spectrometric single reaction monitoring. The lower limit of quantitation was 1.09 and 1.0 ng/mL for erlotinib and OSI-420, respectively.

Plasma samples were analyzed for concentrations of paclitaxel by use of a validated liquid chromatography-tandem mass spectrometry procedure. Briefly, aliquots of the thawed samples were mixed with an internal standard and methanol and extracted by protein precipitation. The supernatant was analyzed. Separation of analytes was accomplished by reverse-phase high-performance liquid chromatography followed by mass spectrometric single reaction monitoring. The lower limit of quantitation for the analyte was 5.00 ng/mL.

Plasma samples were analyzed for concentrations of paclitaxel by use of a validated liquid chromatography-tandem mass spectrometry procedure. Briefly, aliquots of the thawed samples were mixed with an internal standard and methanol and extracted by protein precipitation. The supernatant was analyzed. Separation of analytes was accomplished by reverse-phase high-performance liquid chromatography followed by mass spectrometric single reaction monitoring. The lower limit of quantitation for the analyte was 5.00 ng/mL.

Plasma samples were analyzed for concentrations of total platinum from carboplatin by use of a validated graphite furnace atomic absorption (GFAA) procedure. Briefly, aliquots of the thawed samples were transferred to cups and injected directly on GFAA. The limit of quantitation was 50.00 ng platinum/mL.

Pharmacodynamic assays in skin
To assess the pharmacodynamic effects of treatment with an EGFR tyrosine kinase inhibitor, normal skin as a surrogate tissue was procured for evaluation at baseline and then serially. Biopsies of normal skin were done pretreatment and before courses 2 and 3. The antibodies and immunohistochemical methods used are as follows. Antibodies. The following antibodies were used: EGFR monoclonal antibody (Zymed, San Francisco, CA); phospho-EGFR (Tyr1173) monoclonal antibody (Calbiochem, San Diego, CA); p27 kip1 monoclonal antibody (Zymed); polyclonal anti–phospho-extracellular signal-regulated kinase (ERK) Thr202/Tyr204 antibody (Cell Signaling Technology, Beverly, MA); and polyclonal ERK1 (C-16, also stains ERK2) antibodies (Santa Cruz Biotechnology, Santa Cruz, CA). Immunohistochemistry. Sections were heated to 60°C and dehydrated in xylene and graded alcohols. Antigen retrieval was done with 0.01 mol/L citrate buffer at pH 6.0 at 95°C (for phospho-EGFR, p27, ERK, and phospho-ERK), and proteinase K for 5 min for EGFR.

Sections were incubated in primary antibody diluted in 50 mmol/L Tris-HCl (pH 7.6), 150 mmol/L NaCl, 0.1% Tween 20 (TBS-T) containing 1% ovalbumin and 1 mg/mL sodium azide (12 h), followed by incubations with biotinylated secondary antibody for 15 min, peroxidase-labeled streptavidin for 15 min (LSAB-2 System, Dako Corp., Carpinteria, CA), and diaminobenzidine and hydrogen peroxide chromogen substrate (Dako) along with 3,3’-diaminobenzidine enhancer (Signet, Dedham, MA) for 10 min. Slides were counterstained with hematoxylin and mounted.

Quantitation. The staining intensities for EGFR, phospho-EGFR, ERK, and phospho-ERK were semiquantitatively assessed on a 0 to 3+ scale, with <10% staining as 0, 10% to <20% staining as 1+, 20% to 50% staining as 2+, and ≥50% staining as 3+. For p27, the grading was based on the number of cells staining positively for antibody out of 500 cells.

Pharmacokinetic and pharmacodynamic analysis
Paclitaxel and total platinum pharmacokinetics were examined using noncompartmental analytic methods with WinNonLin Enterprise, version 4.1 software (Pharsight Corp., Mountain View, CA) and actual sample times. The terminal rate constant, λz, was calculated using (at least) three quantifiable time points in each plasma profile. The AUC0–inft for paclitaxel was calculated using the linear trapezoidal method and extrapolated to infinite time using the relationship: AUC extrapolated = C0f/λz (19). The area under the curve for total platinum was calculated using the last sample time point, which occurred at 48 h following the infusion (AUC0–48h). In addition to noncompartmental analysis, compartmental methods were employed to determine the α and β half-lives for paclitaxel. A two-compartmental model that assumed first-order elimination was observed to give the best fit based on the fractional coefficients of variation.

For erlotinib and OSI-420, the duration of the plasma sampling following the first dose (study day 3) was determined to be insufficient for accurate assessment of pharmacokinetic variables. Samples were collected up to 8 h following the dose, which was too short based on the ~24-h half-life observed for erlotinib in cancer patients. This was of little consequence to the analysis of the study data because the erlotinib pharmacokinetic data collected in the presence of concomitant paclitaxel and carboplatin dosing were after multiple consecutive days of erlotinib dosing, when steady-state concentrations would be expected. Therefore, for erlotinib and OSI-420, pharmacokinetic variables were calculated from the course 2 day 1 plasma sample data using noncompartmental methods assuming steady state and included Cmax, Tmax, C24h, and AUC0–24h. OSI-420 was calculated using the log-linear trapezoidal rule.

Statistical analysis
Paclitaxel and total platinum pharmacokinetic variables (Cmax, and AUC0–inft or AUC0–48h) on course 1, day 1 and course 2, day 1 were compared within each patient using a paired t test, thus removing interpatient variability from the analyses. Given that doses of paclitaxel and carboplatin were not always the same in courses 1 and 2 due to dose reductions, comparisons of pharmacokinetic variables were made using dose-normalized values. A significance level of 0.05 was used for all analyses. All statistical analyses were done using the SAS version 8.2 statistical software program (SAS Institute, Cary, NC).

Results

General
Twenty patients, whose pertinent characteristics are summarized in Table 1, received 136 total courses of erlotinib, paclitaxel, and carboplatin. The total numbers of new patients and fully evaluable courses at each erlotinib dose level, as well as the rates of DLT as a function of dose level, are detailed in Table 2. Dose reductions, due to toxicity that resulted in patients
being treated with multiple intermediate dose levels, are outlined in Table 2. Eleven patients continued to receive erlotinib alone after treatment with the study regimen. 

Erlotinib dose escalation proceeded in the following manner. Six new patients were treated at the first dose level of 100 mg erlotinib with paclitaxel 225 mg/m² and carboplatin AUC 6 mg/min/mL. One of six patients at the first dose level experienced DLT, having grade 3 diarrhea despite optimal supportive therapy, which was attributed to erlotinib exposure. Another patient had grade 4 neutropenia longer than 5 days; however, this did not meet the protocol criteria for DLT because it was felt to be an expected effect of the cytotoxic therapy rather than erlotinib. Dose escalation of erlotinib was permitted if two or fewer DLTs occurred in a cohort of six patients, and thus the next dose level explored was 150 mg erlotinib with paclitaxel 225 mg/m² and carboplatin AUC 6 mg/min/mL. Two of five patients treated at the second dose level experienced intolerable grade 3 rash, whereas one patient experienced febrile neutropenia in association with a hemorrhagic skin rash. Because the incidence of DLT exceeded the rate predefined for that of the maximum tolerated dose, an intermediate dose level consisting of erlotinib 125 mg/d, paclitaxel 225 mg/m², and carboplatin AUC 6 mg-min/mL was evaluated. No DLTs were observed in the first three patients treated at this intermediate dose level and, therefore, additional patients were enrolled with no DLTs among nine patients treated. Therefore, the recommended phase II dose level was erlotinib 125 mg/d, paclitaxel 225 mg/m², and carboplatin AUC 6 mg-min/mL.

**Hematologic toxicity**

Myelosuppression, particularly neutropenia, was the principal hematologic toxicity of the erlotinib/paclitaxel/carboplatin regimen. The median, range, and distribution of the nadir absolute neutrophil count and platelet counts as a function of dose level are displayed in Table 3. The absolute neutrophil count nadir during the first course typically occurred between days 6 and 14 (median 13 days), with recovery by the planned start date of the second course. Neutropenia of grade 3 or 4 severity occurred in 48 of 136 (35%) courses and was of dose limiting severity in 3 (2%) courses. Thrombocytopenia with a platelet count <25,000/µL was observed in 2 of 136 (1.5%) courses, with both instances occurring beyond the first course. The first cohort (erlotinib 100 mg, paclitaxel 225 mg/m², and carboplatin AUC 6 mg-min/mL) was associated with brief grade 3 or 4 neutropenia in 15 of 33 (45%) evaluable courses whereas one patient experienced prolonged neutropenia in the first course and another experienced grade 4 neutropenia with fever in course 3. A total of 26 courses were administered in the second cohort (erlotinib 150 mg, paclitaxel 225 mg/m², and carboplatin AUC 6 mg-min/mL), of which three were associated with grade 3 neutropenia, five with brief grade 4 neutropenia, one with grade 4 neutropenia and fever, and one with a platelet count <25,000/µL. The third cohort (erlotinib 125 mg, paclitaxel 225 mg/m², and carboplatin AUC 6 mg-min/mL) was complicated by transient grade 3 or 4 neutropenia in 25 of 77 courses, prolonged neutropenia in one course, and a platelet count <25,000/µL in one course.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tr>
<td>No. patients</td>
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<tr>
<td>Median no. courses/patient (range)</td>
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<td>Median age (range), y</td>
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<td>10</td>
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<td>Head and neck</td>
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<tr>
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<td>Bladder, thyroid, penile, colorectal</td>
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Abbreviation: ECOG, Eastern Cooperative Oncology Group.

### Table 2. Dose escalation scheme

<table>
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<tr>
<th>Erlotinib (mg)</th>
<th>Carboplatin AUC (mg min/mL)</th>
<th>Paclitaxel (mg/m²)</th>
<th>Cohort</th>
<th>No. new patients</th>
<th>Patients reduced to this dose</th>
<th>Total patients/ no. courses</th>
<th>New patients with DLT/ total new patients</th>
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Nonhematologic toxicity

Nonhematologic toxicities were mild to moderate in severity in most patients. Cutaneous toxicity and diarrhea were the most common toxicities observed with this regimen and were dose limiting in three patients. The distributions of nonhematologic toxicities as a function of both grade and dose level are listed in Table 4.

Cutaneous toxicity, which was experienced by 18 of 20 (90%) evaluable patients, was generally asymptomatic or minimally symptomatic. Intolerable grade 3 skin rash was observed in two patients who received treatment with erlotinib 150 mg/d; one of these individuals developed a hemorrhagic rash. Grade 1 or 2 rash occurred in 70% of courses with 19 of 33 (58%) courses affected in cohort 1, 16 of 26 (62%) courses affected in cohort 2, and 61 of 77 (79%) courses affected in cohort 3. The rash typically involved the face and upper trunk and was characterized by maculopapular and pustular acneiform lesions on an erythematous base. The onset of rash was often within the first 10 days of treatment, with some patients resolving gradually over weeks and others continuing throughout all cycles. The use of supportive agents, including topical and systemic corticosteroids and antibiotics, was permitted and, in some cases, ameliorated symptoms. Diarrhea occurred in 11 patients and was characterized as loose or watery stools without blood, mucous, fever, or tenesmus. Grade 1 or 2 diarrhea occurred in 35 of 136 (26%) courses and was either self-remitting or improved following the use of loperamide.

One patient experienced grade 3 diarrhea in cohort 1 in spite of optimal supportive care and required two successive dose reductions of erlotinib. A second patient in cohort 3 (erlotinib 125 mg/d) experienced grade 3 diarrhea in course 3, which responded to supportive management. Nausea and vomiting were also observed in patients treated with erlotinib, paclitaxel, and carboplatin but were not dose limiting. Grade 1 and/or 2 nausea or vomiting occurred in 22 (16%) and 12 (9%) of 136 courses, respectively, and was typically managed with phenothiazines or serotonin 5-HT3 receptor antagonists. Other toxicities which were not dose limiting included peripheral neuropathy, fatigue, arthralgia, myalgia, dysgeusia, and weight loss.

Antineoplastic activity

Three confirmed partial responses were observed. Partial responses were noted in two previously untreated patients with metastatic NSCLC who received treatment as part of the first and third cohorts (erlotinib doses of 100 and 125 mg, respectively). The response durations were 7 and 12 months. A partial response lasting 8 months was also observed in a 51-year-old previously untreated female with head and neck cancer. The patient was treated with erlotinib 125 mg/d, paclitaxel 225 mg/m², and carboplatin AUC 6 mg/C1/C1 min/mL. Stable disease for 9 months was observed in two previously untreated patients with NSCLC and head and neck cancer.

Table 3. Hematologic toxicity

<table>
<thead>
<tr>
<th>Erlotinib dose level/cohort (mg)</th>
<th>No. patients (courses)</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
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<td></td>
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<td>Median nadir</td>
<td>Gr. 3</td>
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<td>290 (60-790)</td>
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<td>150/2</td>
<td>5 (26)</td>
<td>610 (40-1,480)</td>
<td>3 (1)</td>
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Abbreviations: ANC, absolute neutrophil count; heme, hematologic; Gr, grade.

*Toxicities were defined as dose limiting if attributed to erlotinib exposure.

Median values (ranges) for all courses. Values expressed as μL (range).

Prolonged neutropenias in both cases were attributed to cytotoxic therapy rather than to erlotinib and therefore not scored as dose-limiting toxicities.

Table 4. Nonhematologic toxicity

<table>
<thead>
<tr>
<th>Erlotinib dose level/cohort (mg)</th>
<th>No. patients (courses)</th>
<th>Rash grade</th>
<th>Diarrhea grade</th>
<th>Nausea grade</th>
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<td>6 (33)</td>
<td>19 (4)</td>
<td>0 (0)</td>
<td>13 (1)</td>
<td>1 (1)</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>125</td>
<td>9 (77)</td>
<td>61 (7)</td>
<td>0 (0)</td>
<td>16 (4)</td>
<td>1 (0)</td>
<td>15 (4)</td>
<td>1 (0)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>150</td>
<td>5 (26)</td>
<td>16 (1)</td>
<td>2 (2)</td>
<td>6 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
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Abbreviations: Arth, arthralgias; Myal, myalgias.
Pharmacokinetics

Plasma samples for pharmacokinetic studies were obtained from 19 patients for paclitaxel, carboplatin, and erlotinib, principally to detect relevant drug-drug interactions. Figures 1 and 2 display $C_{\text{max}}$ and AUC values for paclitaxel and platinum, respectively, in the presence and absence of erlotinib. A one-sample (paired) $t$ test was done to compare dose-normalized $C_{\text{max}}$ and AUC values between course 1 (without erlotinib) and course 2 (with erlotinib). For paclitaxel, there were no significant differences in dose-normalized $C_{\text{max}}$ ($P = 0.17$) or AUC$_{0-\text{inf}}$ ($P = 0.14$) among 18 patients for whom data from both courses were available. There were no significant differences between dose-normalized total platinum $C_{\text{max}}$ values in the presence and absence of erlotinib ($P = 0.69$) among 16 patients for whom data from both courses were available, although AUC$_{0-48\text{h}}$ values were significantly higher, 10.6% on average, in the presence of erlotinib ($P = 0.02$). Figure 3 shows dose-normalized erlotinib steady-state $C_{\text{max}}$ and AUC$_{0-24\text{h}}$ values in the presence and absence (historical data) of paclitaxel and carboplatin. Paired $t$ tests were done to compare steady-state AUC$_{0-24\text{h}}$ and $C_{\text{max}}$ values between the present study and the historical monotherapy data (20). Data were available from 16 patients following erlotinib administration in the presence of carboplatin and paclitaxel for $C_{\text{max}}$ and from 13 patients for AUC$_{0-24\text{h}}$. The historical data set for erlotinib $C_{\text{max}}$ and AUC$_{0-24\text{h}}$ as monotherapy consisted of data from 24 and 20 patients, respectively.
23 patients, respectively. There were no significant differences in erlotinib dose-normalized $C_{\text{max}}$ ($P = 0.94$) or AUC$_{0-24h}$ ($P = 0.38$) when administered with and without paclitaxel and carboplatin. Similar results were obtained for OSI-420, with $P$ values for the differences between erlotinib monotherapy and combination therapy being 0.95 and 0.78.

**Correlative studies in skin**

Serial samples of normal skin were obtained in 12 patients to assess the effects of erlotinib on EGFR and downstream signaling proteins. There were no consistent effects shown in expression of EGFR, phospho-EGFR, ERK, or phospho-ERK following treatment with the investigational regimens. The expression of p27 increased in eight patients following treatment with erlotinib, and two of these patients had confirmed partial responses.

**Discussion**

Aberrant EGFR expression is detected in many solid tumors and is associated with poor disease outcome (1–3). EGFR activation can promote a malignant phenotype and was therefore identified as an attractive therapeutic target for anticancer drug development. The rationale for the combination of erlotinib with carboplatin and paclitaxel was based on favorable interactions between erlotinib and platinum compounds shown in preclinical studies and the known single agent activity of erlotinib in NSCLC, ovarian cancer, and head and neck cancer, all of which are known to respond to platinum-based therapies (16, 17).

This phase I, pharmacologic, and biological study was designed to evaluate the feasibility of administering erlotinib daily with paclitaxel and carboplatin given i.v. every 3 weeks. The principal toxicities of this regimen were neutropenia, skin rash, and diarrhea, although hematologic toxicity was attributed predominantly to the effects of cytotoxic therapy rather than erlotinib. Repeated administration of the regimen at its recommended phase II dose level (erlotinib 125 mg/d, paclitaxel 225 mg/m$^2$, and carboplatin AUC 6 mg-min/mL) was tolerable.

Dose-normalized pharmacokinetic variables reflecting drug exposure were used because there were dose reductions of both erlotinib and chemotherapy for some patients between courses 1 and 2. Although the pharmacokinetics of paclitaxel were not significantly different in the presence and absence of erlotinib, the shown results for carboplatin are less clear. Whereas the carboplatin $C_{\text{max}}$ values were not significantly different between courses 1 and 2, AUC$_{0-48h}$ values increased by 10.6%, on average, in course 2 ($P = 0.02$). Nevertheless, considerations in interpreting these results should include the fact that only total platinum, instead of both total and free platinum concentrations, was measured, and some patients received dose reductions of paclitaxel and erlotinib in course 2. From a clinical perspective, however, it is unlikely that the higher exposure to total platinum affected the ability to administer carboplatin because only two patients required dose reduction due to myelosuppression following course 1. There was no significant difference in pharmacokinetic variables reflecting erlotinib exposure ($C_{\text{max}}$ and AUC$_{0-24h}$) observed following concomitant administration of erlotinib with paclitaxel and carboplatin and those resulting from patients receiving erlotinib monotherapy (historical data; ref. 20).

The results of this phase I and pharmacokinetic study indicate that daily treatment with erlotinib in combination with paclitaxel and carboplatin administered every 3 weeks i.v. is feasible and generally well tolerated over multiple cycles. The maximum dose of erlotinib that could be administered with full doses of paclitaxel and carboplatin was 125 mg/d. Although erlotinib could not be administered at the standard single-agent dose of 150 mg/d in this combination study, skin rash, a potential surrogate marker of activity, was observed consistently at the 125 mg dose level (21). The tolerance of a similar regimen was substantiated in a phase III study of 1,059 patients with advanced NSCLC receiving first-line therapy consisting of paclitaxel and carboplatin with or without erlotinib (TRIBUTE—Tarceva responses in conjunction with paclitaxel and carboplatin; ref. 22). No survival benefit or improvement in response rate versus chemotherapy alone was observed in this trial. Some notable differences in the doses of erlotinib and paclitaxel were, however, apparent in this...

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**Fig. 3.** Dose normalized erlotinib steady-state $C_{\text{max}}$ and AUC$_{0-24h}$ in the presence and absence (historical) of concomitant paclitaxel and carboplatin. Abbreviations: E, erlotinib; P, paclitaxel; C, carboplatin; AUC$_{0-24h}$, Area under the curve for erlotinib that was calculated through the last sample time point, which occurred at 24 h post-treatment.
study. Patients received 200 mg/m² of paclitaxel instead of 225 mg/m² used in the current phase I study, possibly accounting for better hematologic tolerance and, furthermore, the ability to administer the standard single-agent dose of erlotinib (150 mg). There are several reasons why the current phase I study failed to show tolerance of the 150 mg erlotinib dose level, including the fact that all five patients evaluated at this dose level had received prior therapy, thus representing a more extensively pretreated population compared with the TRIBUTE study, in which patients had not received prior chemotherapy for advanced disease. In addition, patients in the current phase I trial received higher doses of paclitaxel consistent with a more aggressive but arguably less well tolerated regimen used for NSCLC. Furthermore, as with all limited data sets, greater variations in results are possible due to a small sample size.

The current phase I study was important as it showed the feasibility of administering paclitaxel and carboplatin with erlotinib. Randomized phase III trials have, however, failed to show benefit for the addition of small molecules to chemotherapy regimens in NSCLC. Along with the TRIBUTE study, three additional trials of chemotherapy in combination with EGFR tyrosine kinase inhibitors have yielded negative results in advanced NSCLC although none of these studies selected patients on the basis of EGFR dependence (23–25). Erlotinib administered as a single agent after first- or second-line chemotherapy has, however, shown survival benefit in NSCLC in comparison with placebo (National Cancer Institute of Canada BR.21), resulting in the regulatory approval of erlotinib in the United States and worldwide (26). The negative results of randomized phase III trials of chemotherapy and EGFR tyrosine kinase inhibitors in advanced NSCLC suggest that the concurrent administration of small-molecule EGFR tyrosine kinase inhibitors does not augment standard cytotoxic therapeutic regimens in unselected patients. Determination of determinants of activity and alternate schedules and/or sequential administration of agents may be warranted given the single-agent activity of erlotinib in NSCLC. Furthermore, as increasing data become available on the presence of EGFR tyrosine kinase domain mutations, this will need to be taken into consideration in the design of future clinical trials to select patients with EGFR dependence. Pathway dependence was pivotal in the studies that confirmed the efficacy of trastuzumab in patients with metastatic breast cancer, a finding which might otherwise have been missed in a population unselected for HER2/neu amplification (27, 28). The CALGB-30406 trial has used a regimen involving paclitaxel, carboplatin, and erlotinib to determine activity in a chemotherapy-naïve select population of patients with stage IIIIB or IV NSCLC in comparison with erlotinib alone and relationships between EGFR mutations and end points reflecting clinical benefit will be evaluated. Future studies evaluating the combination of erlotinib, paclitaxel, and carboplatin should also be considered for other solid tumors, including ovarian and head and neck cancers.

References

Phase I, Pharmacokinetic, and Biological Study of Erlotinib in Combination with Paclitaxel and Carboplatin in Patients with Advanced Solid Tumors


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