



Phase I study of gefitinib, oxaliplatin, 5-fluorouracil, and leucovorin (IFOX) in patients with advanced solid malignancies

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Summary

Purpose: A phase 1 study of gefitinib in combination with oxaliplatin, 5-fluorouracil and leucovorin (IFOX) was conducted to evaluate the safety and feasibility of this regimen. **Patients and Methods:** Patients with advanced solid malignancies were treated with escalating doses of gefitinib (250 mg or 500 mg once daily) in combination with FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin). The initial dose of oxaliplatin was 70 mg/m² with sequential dose escalation to 85 mg/m². **Results:** Sixteen patients received a total of 138 14-day courses of daily gefitinib in combination with FOLFOX. Escalation of gefitinib from 250 mg/d to 500 mg/d with FOLFOX was well-tolerated. In addition, no severe toxicities precluded subsequent dose escalation of oxaliplatin from 70 mg/m² to 85 mg/m² at which no dose-limiting toxicity was seen. No further dose escalation was performed as this represented the oxaliplatin dose administered in the standard FOLFOX-4 regimen. The most predominant toxicity was diarrhea, which was well controlled with oral antidiarrheal agents. Four partial remissions occurred in patients with metastatic colorectal cancer. **Conclusions:** Gefitinib as a 500 mg daily continuous dose was well tolerated in combination with full doses of FOLFOX-4.

Epidermal growth factor receptor (EGFR) is expressed in many human epithelial malignancies including non small-cell lung (NSCLC), breast, colorectal, and head and neck cancers [1]. High expression of EGFR has been associated with metastasis, late-stage disease, resistance to hormonal and cytotoxic therapies, and poorer prognosis.

Several antibodies and small molecule drugs which block EGFR signaling pathways have been developed as potential anticancer therapies [2]. Gefitinib (ZD1839, Iressa; AstraZeneca, London, United Kingdom) is an orally active, selective EGFR-tyrosine kinase inhibitor that blocks ATP-binding [3, 4].

In preclinical studies, gefitinib has antitumor activity against several human cancer cell lines expressing EGFR, and enhanced the antitumor effects of both chemotherapy and radiation in some cell lines and xenografts of human colon, non-small cell lung (NSCLC), and prostate cancers [5–9].

In clinical studies, gefitinib has diarrhea as the dose-limiting toxicity at 700–1000 mg/d [10, 11]. Skin biopsies were obtained from some patients enrolled in these phase I trials to evaluate the pharmacodynamic effects of gefitinib. Gefitinib was shown to suppress EGFR phosphorylation in EGFR-expressing skin cells, to in-

hibit mitogen-activated protein kinase (MAPK) and to reduce keratinocyte proliferation index. Concomitantly, gefitinib increased the expression of the cyclin dependent kinase, p27^{KIP1}, implicated in G₁ growth arrest and increased apoptosis. These effects of gefitinib on EGFR activation and downstream receptor-dependent processes demonstrated that gefitinib inhibits EGFR at doses below the maximally tolerated dose. Gefitinib has been approved in the United States and other countries as a single agent for patients with advanced NSCLC after failure of prior chemotherapies, based on Phase II trials in that disease [12].

FOLFOX combines 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin, and is a highly active chemotherapy regimen for patients with advanced colorectal cancer [13, 14]. Toxicities of FOLFOX include myelosuppression, diarrhea, nausea, vomiting and cumulative peripheral sensory neuropathy. We embarked on a Phase I study of FOLFOX plus gefitinib because of the high frequency of EGFR expression in colorectal cancers and preclinical evidence of potentiation by gefitinib of chemotherapeutic drugs, including oxaliplatin. Since diarrhea is dose limiting with gefitinib, we preferred to combine this agent with oxaliplatin rather than irinotecan [4, 15]. This

phase I safety and feasibility study of gefitinib in combination with cytotoxic therapy was designed to assess daily continuous dosing of gefitinib with FOLFOX in patients with refractory solid malignancies. Sequential dose-escalations of gefitinib and then oxaliplatin were performed to assess tolerability of the IFOX combined regimen.

Patients and methods

Patient selection

Patients were eligible for this study if they had an advanced solid malignancy for which no curative therapy was available; were age 18 years or older; had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; life expectancy > 3 months; and adequate hematopoietic (absolute neutrophil count [ANC] $\geq 1,500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$), hepatic (total bilirubin ≤ 1.5 mg/dL, transaminases ≤ 2.5 times institutional normal upper limit), and renal (creatinine within normal institutional limit or creatinine clearance ≥ 60 mL/min) functions. Patients were not eligible if they had more than 3 prior chemotherapy regimens; any chemotherapy, investigational agents, or radiation therapy within 4 weeks (6 weeks for nitrosureas and mitomycin); prior pelvic or whole abdominal radiotherapy; peripheral neuropathy; active brain metastasis; or co-existing medical problem of sufficient severity to limit compliance with the study. This trial was reviewed and approved by the Stanford University Panel on Human Subjects in Research. Before treatment, patients gave written informed consent according to federal and institutional guidelines.

Dosage and drug administration

Toxicities were graded by the NCI Common Toxicity Criteria, version 2.0, with the exception of neurotoxicity. Neurotoxicity was reported using the following grading scale: grade 0, no symptoms; grade 1, paresthesias/dysesthesias of short duration that resolved and did not interfere with function; grade 2, paresthesias/dysesthesias interfering with function but not activities of daily living; grade 3, paresthesias/dysesthesias with pain or with functional impairment that also interfere with activities of daily living; and grade 4, persistent paresthesias/dysesthesias that were disabling or life-threatening. Dose limiting Toxicities (DLT) were defined as (1) grade 4 neutropenia ≥ 5 days or with fever; (2) grade 4 thrombocytopenia; (3) other grade ≥ 3 toxicity (except alopecia, diarrhea in the absence of oral antidiarrheals, and nausea/vomiting in the absence of antiemetics); (4) delay

of > 2 consecutive weeks of treatment due to persistent toxicity.

For patients in Cohort 1, the starting dose of gefitinib was 250 mg (G250) administered orally on a daily basis beginning with day 1 of cycle 2 to allow for paired observations of toxicities of the first and second cycle. Similarly, in Cohorts 2 and 3, patients received chemotherapy alone on the first cycle, and gefitinib was added on the second and subsequent cycles. The chemotherapy was administered as per the standard FOLFOX regimen every 14 days. The starting dose of oxaliplatin for patients in Cohort 1 was 70 mg/m² (O70) administered intravenously over 2 hours (hours 0–2) on day 1. The dose of LV and 5-FU was the same for all cohorts. LV 200 mg/m² was administered intravenously over 2 hours (hours 0–2) on days 1 and 2. Following the completion of the oxaliplatin and LV infusions, 5-FU 400 mg/m² was administered as an intravenous bolus on days 1 and 2 followed by 5-FU 600 mg/m² administered intravenously over 22 hours (hours 2–24) on days 1 and 2. Dose escalation of gefitinib and oxaliplatin then proceeded, with Cohort 2 receiving gefitinib 500 mg daily oral dosing in combination with oxaliplatin at 70 mg/m², (G500/O70), and Cohort 3 receiving gefitinib 500 mg daily oral dosing with the oxaliplatin dosage increased to 85 mg/m² (G500/O85). Inpatient dose escalation was permitted on the study, if less than 1 of 3 patients or equivalent did not experience DLT in the successive cohort.

The number of patients per cohort or dose level was based on any DLT experienced during cycles 1 and 2. A minimum of three patients was entered at each dose level unless DLT was observed. If a DLT was observed in one of the first three patients treated at a particular cohort, up to three additional patients were treated at that dose level. Thus, the maximum tolerated dose (MTD) was defined as one dose level below that which produced two instances of DLT during cycle 1 or 2 and the level at which no more than one of six patients experienced DLT. Cohort 3 was the highest proposed dose level because it included full-doses of the components of FOLFOX, hereafter referred to as FOLFOX-4 when full doses were administered. If this dose level produced no more than one of six patients with DLT, it was defined as the recommended phase II dose.

Patients were instructed to take gefitinib approximately 24 hours apart and to keep a daily written log of when gefitinib was taken and the frequency of diarrhea, nausea, and vomiting.

Drug administration

The Division of Cancer Treatment and Diagnosis (National Cancer Institute, Bethesda, MD) supplied

Table 1. Patient characteristics of the IFOX phase I trial

Characteristic	No. of patients
Total	16
Age, years: median (range)	51 (31–61)
Gender, male:female	10:6
Tumor Type	
Colorectal	12
Unknown Primary	3
Non-small cell Lung	1
Number of Prior chemotherapy regimens	
0	4
1	4
2	3
3	5

gefitinib in 250 mg tablets and oxaliplatin in 50- and 100-mg vials. After reconstitution, oxaliplatin was infused over 2 hours through a central venous or peripheral catheter. Prophylactic oral granisetron 2 mg was administered prior to each dose of oxaliplatin.

Pretreatment and follow-up studies

A medical history, physical examination, complete blood count, electrolytes, creatinine, total bilirubin, ALT, AST, and LDH were performed at the start of therapy and prior to initiating each cycle. Tumor markers were obtained when applicable. For women of child-bearing age, a serum pregnancy test was obtained to rule-out pregnancy prior to the start of therapy. Hematologic tests were obtained on Day 8 of each cycle. Sites of disease were evaluated before treatment and after every fourth cycle for response on the basis of RECIST criteria.

Results

16 patients were enrolled between July 2001 and March 2002 and all were assessable for toxicity. Patient demographics are listed in Table 1. A total of 138 cycles of treatment were administered with a median number of 9 cycles per patients (range, 3 to 14 cycles). There are no patients who remain on study.

Dose escalation and dose-limiting toxicity

One patient in Cohort 1 (G250/O70/5-FU) developed acute renal failure during cycle 2 that was considered unrelated to drug, as he was found to have bilateral ureteral obstruction from disease. His renal failure resolved with placement of ureteral stents, and he remained on study. As the patient did not complete all of the prescribed treatment in cycle 2, a fourth patient was enrolled in Cohort 1. At the

second dose level (G500/O70/5-FU), one patient developed a central line infection requiring hospitalization for antibiotics. As the indication for placement of the central line was to receive the study treatment, this was deemed to be a treatment-related toxicity, and therefore constituted a DLT. This cohort was therefore expanded to six patients, with no additional DLTs. In Cohort 3 (G500/O85/5-FU), one patient had a DLT comprised of the combination of grade 3 diarrhea, grade 3 dehydration, and grade 3 hypokalemia, requiring hospitalization for intravenous fluids and electrolytes. This cohort was expanded to six patients, and no additional DLT was observed. One patient in Cohort 3 developed grade 3 diarrhea during cycle 2. However, this patient was not taking antidiarrheal therapy, as required to meet the predefined criteria for DLT. Upon starting loperamide, the patient's diarrhea resolved within 24 hours. Thus, dose level 3 was defined as the recommended phase II dose for daily gefitinib administered in combination with full-dose FOLFOX-4.

Toxicities

Hematologic toxicities. A summary of the neutropenia experienced by patients in any cycle is listed in Table 2. Hematologic toxicity was generally mild. There was one case of grade 4 neutropenia at each dose level. Only one case was also associated with fever, in a patient receiving dose level 3 during a hospitalization for *C. difficile* colitis. This occurred during his seventh cycle of treatment and therefore did not constitute a DLT. There was only one case of grade 2 thrombocytopenia that occurred in a patient receiving dose level 2. This was not associated with any bleeding events. No grade 3 or 4 thrombocytopenia was observed. Grade 2 anemia was noted in patients at all dose levels. Only one case of grade 3 anemia occurred, in a patient receiving dose level 2. No grade 4 toxicity or need for blood transfusion occurred at any dose level.

Gastrointestinal toxicities. No grade 4 gastrointestinal toxicities were seen. Nausea and diarrhea were the most common gastrointestinal grade 3 toxicities observed, Table 2. In addition, instances of grade 3 nausea, vomiting, and diarrhea were often accompanied by grade 3 dehydration, hypokalemia, and anorexia. The highest number of such cases occurred in patients receiving dose level 3, though only 1 case occurred during the first 2 cycles and constituted a dose-limiting toxicity.

Biochemical toxicities. Two patients experienced grade 3 elevations in transaminases without clinical sequelae. One patient treated at dose level 1 had return of his transaminases to grade 1 following a 2-week delay before continuing with treatment. His treatment was resumed at a dose reduction of oxaliplatin to 60 mg/m² without further

Table 2. Number of patients experiencing grade 1, 2, 3, or 4 toxicities for any cycle of treatment, by treatment cohort and grade of toxicity. No grade 4 non-hematologic toxicities were observed

	Cohort 1 (G250/O70/5-FU)	Cohort 2 (G500/O70/5-FU)	Cohort 3 (G500/O85/5-FU)
Number of patients	4	6	6
Total number of cycles	42	46	50
Neutropenia			
Gr 2	0	2	2
Gr 3	2	1	2
Gr 4	1	1	1
Nausea			
Gr 1	1	2	1
Gr 2	2	4	2
Gr 3	1	0	3
Vomiting			
Gr 1	0	3	1
Gr 2	2	1	4
Gr 3	0	1	1
Peripheral Neuropathy			
Gr 1	2	5	5
Gr 2	0	0	1
Stomatitis			
Gr 1	1	1	3
Gr 2	0	3	2
Fatigue			
Gr 1	3	2	0
Gr 2	1	3	4
Gr 3	0	0	1
Diarrhea			
Gr 1	0	2	0
Gr 2	1	1	2
Gr 3	2	2	4
Skin Rash			
Gr 1	2	1	0
Gr 2	1	5	2
Abdominal Cramping			
Gr 2	3	1	2
Infection			
Gr 2	1	0	0
Gr 3	0	1	1
Transaminitis			
Gr 3	1	0	1
Dehydration			
Gr 2	0	0	1
Gr 3	0	1	3
Hypokalemia			
Gr 1	1	1	0
Gr 2	0	0	0
Gr 3	0	2	4

hepatotoxicity. A patient treated at dose level 3 experienced grade 3 elevations in transaminases during her fifth cycle for which a prolonged delay in treatment was required before return of her transaminases to grade 1. Her

treatment was resumed at a dose reduction of oxaliplatin to 70 mg/m². However she experienced grade 2 elevations in her transaminases at this dose level requiring a prolonged recovery time to grade 1, and therefore withdrew from study.

Other toxicities. An acneiform rash was seen in 11 out of the 16 patients. Three patients had asymptomatic rash (grade 1), while the remaining 8 patients reported some pruritis associated with rash involving <50% of their body (grade 2). The typical distribution was involving the face, upper chest and back. For the majority of patients, the rash was minimally to mildly symptomatic requiring no specific intervention. For patients who described the rash to be associated with bothersome pruritis or cosmetic appearance, a course of oral cephalexin 500 mg orally twice a day was prescribed, usually resulting in improvement within a few days.

Peripheral neuropathy was described by almost all patients, but in general was mild. Only 1 patient described persistent neuropathy that affected function (grade 2), for which the dose of oxaliplatin was reduced to 65 mg/m² without further progression of symptoms.

Three patients had clinical manifestations of hypersensitivity reactions following administration of oxaliplatin. These reactions occurred during the ninth infusion of oxaliplatin in two patients, and during the eleventh infusion in the third patient. Symptoms included flushing and acute onset of pruritis and were limited to grade 1 and 2 toxicities. Subsequent doses of oxaliplatin in these patients were pre-treated with antihistamines and corticosteroids without further reactions.

Alopecia was seen in five of the 16 patients. All occurrences of alopecia were partial, involving <50% hair loss.

Comparison of toxicities in cycles 1 and 2

Table 3 presents the data comparing the toxicities recorded during the first cycle of treatment, consisting of FOLFOX without gefitinib, to the second cycle which included gefitinib (IFOX). Increased diarrhea was noted, as expected, when gefitinib was added to the FOLFOX regimen. Only one patient had grade 3 diarrhea while using supportive measures. Although diarrhea was worsened, the incidence of stomatitis was identical between the first and second cycles, with only one grade 1 and one grade 2 toxicity noted in each cycle. Nausea and vomiting were similarly not increased by the addition of gefitinib. The characteristic skin rash of gefitinib appeared soon after the drug was begun in seven patients, and in four additional patients after the second cycle of treatment, Tables 2 and 3. Neutropenia was more prominent with the second cycle of treatment, but this may simply reflect a cumulative effect

Table 3. Comparison of toxicities noted in the first cycle of FOLFOX alone compared to the second cycle of gefitinib added to FOLFOX (IFOX), N = 16 patients

Toxicity and grade	Cycle 1 (FOLFOX)	Cycle 2 (IFOX)
ANC		
1	1	4
2	1	3
3	0	1
4	0	2
Platelets		
1	1	2
Nausea		
1	10	12
2	3	1
3	0	1
Vomiting		
1	9	6
2	3	3
Neuropathy		
1	4	5
Fatigue		
1	3	6
2	2	1
Diarrhea		
1	4	5
2	1	3
3	0	2
Derm		
1	0	2
2	0	5
Stomatitis		
1	1	1
2	1	1

of oxaliplatin within the first month of therapy. The incidence of acute neuropathy from oxaliplatin was similar in the first and second cycles, and cumulative neuropathy was not noted in this small series of Phase I patients with limited total number of treatment cycles.

Antitumor responses

Response to therapy was a secondary outcome, and was measured in all patients. All 16 patients treated on the study were assessable for response. Four patients with metastatic colorectal cancer had confirmed partial responses. Eleven of 12 additional patients had evidence of tumor marker decline and/or stable disease after 3 or more cycles of treatment. Of the partial responders, two patients had previously untreated metastatic colorectal cancer, and two patients had colorectal cancer previously treated with 5-FU and irinotecan. Seventy-five percent of responders (3 of 4) and 67% of non-responders (8 of 12) had the acneiform rash. Response durations for patients with rash ranged from 5.2, to 7.6 months. However one of these patients elected to pursue surgical resection of her previ-

ously unresectable liver metastases at 7.4 months, having experienced a large reduction of her tumor burden. The fourth responder, who did not develop a rash, had a response duration of 5.1 months, and then withdrew from the study as he elected to pursue other therapy.

Discussion

EGFR has long been recognized as a promising target for the development of anticancer therapies [2, 4]. Gefitinib and cetuximab are the first EGFR inhibitors to receive FDA approval, with several others in various stages of development.

In this phase I trial of the IFOX regimen, we found the dose of 500 mg per day of gefitinib to be well tolerated with full-doses of FOLFOX-4. One of six patients experienced a dose-limiting toxicity at the highest dose level, establishing this as the recommended phase II dose, as we prospectively designed this trial not to escalate beyond the standard doses of FOLFOX-4 [13].

The predominant toxicity was diarrhea, as anticipated, since gefitinib, 5-FU and oxaliplatin are all associated with this toxicity. The incidence and grade of diarrhea were worse in cycle 2, when gefitinib was added to FOLFOX, compared to the chemotherapy alone in the first cycle. Overall, diarrhea was well controlled with oral antidiarrheal drugs. Hematologic toxicity was similar to that reported for FOLFOX-4 alone, and increased as expected between cycles 1 and 2, probably due to a cumulative effect of oxaliplatin. Alternatively, the additional myelosuppression seen with cycle 2 may indicate a pharmacodynamic interaction between gefitinib and cytotoxic therapy.

DLT was assessed after 2 cycles. While this trial design identified most short-term toxicities, it is acknowledged that potential toxicities that may only manifest after more prolonged dosing may not be revealed through this design. Specifically, an increase in interstitial pneumonitis that has been associated with more protracted use of both gefitinib and oxaliplatin and is uncommon may not appear.

Four partial responses were observed in patients with metastatic colorectal cancer, including two of three with no prior chemotherapy and two of nine with prior therapy for metastatic disease. Both responding patients with prior therapy had been treated with 5-FU and irinotecan.

The rash attributed to gefitinib was cosmetically bothersome or symptomatic, typically pruritic, in the majority of patients. For these patients, the initiation of oral cephalixin 500 mg by mouth twice a day resulted in significant improvement in almost all cases, within several days and without causing increased frequency of stools or other toxicity. Among the responders, a longer duration of response was seen in the three patients who developed a rash compared with the one responder who was

rash-free. Given the small number of patients involved as well as the censoring of two of these patients due to change in treatment, it is difficult to draw any conclusions from this study regarding rash as a predictor of response or clinical benefit.

This study evaluates gefitinib in combination with a chemotherapy regimen known to be active in patients with advanced colorectal cancer, FOLFOX. Currently, there are conflicting data both supporting and refuting a benefit to combining anti-EGFR therapy with cytotoxic therapy. Human tumor xenograft models have suggested a supra-additive effect to combining both anti-EGFR agents with multiple chemotherapy agents including platinum [6–8]. In patients with advanced colorectal cancer, activity has been observed with the monoclonal antibodies cetuximab and EMD 72000 as single agents, whereas the tyrosine kinase inhibitors gefitinib and erlotinib have not produced partial remissions, although stable disease and minor regressions of tumor have been observed [4, 15].

Cetuximab combined with irinotecan has shown tumor regression with a response rate of 22% in patients who had previously shown progression on irinotecan [16, 17]. No trials combining gefitinib with cytotoxic therapy in patients with colorectal cancer have been published to date. However, four randomized, placebo-controlled combination trials have been performed as first line therapy in patients with metastatic non small cell lung cancer (NSCLC), utilizing either gefitinib or erlotinib. These trials have shown no survival benefit for the addition of the EGFR inhibitor to either carboplatin/paclitaxel or cisplatin/gemcitabine chemotherapy [18–20].

There continues to be much debate as to why the pre-clinical data are discordant with the first line combination trials in NSCLC. However, the negative results for chemosensitization by EGFR inhibitors in lung cancers may not be relevant for other tumor types. The evident benefit of cetuximab in reversing resistance to irinotecan in some patients indicates that colorectal cancer in particular may be different from NSCLC with regard to EGFR inhibition and chemosensitivity [16, 17]. Nagourney et al. have found that gefitinib combined with cisplatin promotes apoptosis in primary cultures of human colon cancers while decreasing apoptosis in specimens of non-small cell lung cancers, suggesting that the difference in activity may be tumor-dependent (R. Nagourney, personal communication).

Drug dosage may also be a relevant issue in determining optimal activity of anti-EGFR agents in combination with cytotoxic therapies. The FDA approval of gefitinib for patients with metastatic NSCLC was based on a 250 mg/d dosing. Previous studies in the NSCLC population have studied both the 250 mg/d and 500 mg/d dosing regimens as our study has done. Both doses of gefitinib were assessed in the NSCLC population in combination

with chemotherapy. These studies have not shown any superior benefit of the 500 mg/d dose compared with the 250 mg/d dose, while the 250 mg/d dose had a lower frequency of adverse events [12]. In our phase I study of IFOX, escalation of gefitinib to 500 mg/d was pursued. Until further studies answer how anti-EGFR agents may optimally modulate cytotoxic therapy, we believe that it is reasonable to perform standard dose escalation of these agents in attempt to obtain maximal biologic effect.

In summary, gefitinib as a 500 mg daily continuous dosing in combination with full dose FOLFOX-4 was demonstrated to be safe in patients, though diarrhea was often experienced requiring frequent dosing of oral anti-diarrheals. Further studies are warranted to explore the safety and efficacy of this regimen in patients with colorectal cancer, as well as to investigate surrogate markers for determining patients most likely to benefit from such targeted therapy.

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