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CLINICAL TRIAL REPORT

Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: phase IB trial

Tomislav Dragovich · Mark Huberman · Daniel D. Von Hoff · Eric K. Rowinsky · Paul Nadler · Debra Wood · Marta Hamilton · George Hage · Julie Wolf · Amita Patnaik

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Abstract
Purpose The purpose of this phase IB trial was to evaluate the tolerability, pharmacokinetics and preliminary evidence of antitumor activity of erlotinib plus gemcitabine in patients with pancreatic cancer and other solid tumors.
Patients and methods Patients included those with advanced pancreatic adenocarcinoma or other malignancies potentially responsive to gemcitabine. In the escalating phase of the trial, patients were enrolled in sequential cohorts using 100 or 150 mg oral daily dosing of erlotinib. Gemcitabine dose was 1,000 mg/m^2 weekly ×7 (first cycle), then weekly ×3, every 4 weeks.
Results Twenty-six patients completed at least one course on study. In Cohort IA, at the 100 mg/day dose of erlotinib, three patients have developed grade 3 transaminase elevations. After stricter inclusion criteria were adopted (Cohort IB), no additional events of grade 3 transaminase elevations were observed and the dose of erlotinib was escalated to 150 mg/day (Cohorts IB and IIB) without reaching dose-limiting toxicities. The most common toxicities included diarrhea, skin rash, fatigue and neutropenia. The pharmacokinetic analyses did not reveal any significant interactions between erlotinib and gemcitabine. Objective responses were seen in two patients: cholangiocarcinoma and pancreatic cancer. Patients with unresectable or metastatic pancreatic cancer ($n = 15$) had a median progression-free survival of 289 days, the estimated overall survival of 389 days (12.5 months), and a 1-year survival rate of 51%.
Conclusion The 150 mg/day dose of erlotinib can be safely administered in combination with standard dose gemcitabine in selected patients with pancreatic cancer and other advanced solid tumors. Promising antitumor activity has been observed in patients with pancreatic cancer.

Keywords Erlotinib · EGFR · Gemcitabine · Pancreatic cancer · Clinical trial · Phase I trial

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T. Dragovich (✉) · D. D. Von Hoff
Arizona Cancer Center, University of Arizona,
1515 North Campbell Avenue, Tucson, AZ 85724, USA
e-mail: tdragovich@azcc.arizona.edu

M. Huberman
Beth Israel Deaconess Medical Center,
Boston, MA, USA

E. K. Rowinsky · A. Patnaik
Institute for Drug Development,
Cancer Therapy and Research Center,
San Antonio, TX, USA

P. Nadler · D. Wood · M. Hamilton · G. Hage · J. Wolf
OSI Pharmaceuticals Inc., Boulder, CO, USA

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, with >31,000 deaths per year in the United States [1]. The annual death rate almost equals the annual incidence rate. Gemcitabine therapy was active in patients who failed 5-fluorouracil (5-FU) and has demonstrated an advantage in terms of patient survival and quality of life

when compared to 5-FU as a first-line therapy for advanced pancreatic cancer [2, 3]. The fixed-rate dosing of gemcitabine, based on pharmacokinetic and pharmacodynamic analyses, is another approach that has been investigated [4]. The regimens that combined gemcitabine with 5-FU, irinotecan, cisplatin, oxaliplatin or exatecan although showing promise in phase I and II trials, all failed to demonstrate significant improvement in survival when compared to gemcitabine monotherapy in randomized phase III trials [5–9]. While trials with cytotoxic drugs continue, novel target-based approaches are being actively explored [10, 11]. The epidermal growth factor receptor (EGFR)-dependent signaling pathway plays a critical role in tumor growth and proliferation and has been explored as therapeutic target in epithelial malignancies [12, 13]. The EGFR pathway is of interest as therapeutic target in pancreatic cancer since EGFR was found to be overexpressed by a majority of pancreatic carcinomas [14]. Erlotinib (OSI-774) is a reversible small-molecule inhibitor of HER1/EGFR tyrosine kinase. In preclinical studies, erlotinib has demonstrated additive antitumor effect when combined with cisplatin, paclitaxel, doxorubicin, capecitabine or gemcitabine [15].

The primary objectives of this phase IB trial were to determine the safety, tolerability, pharmacokinetic interactions and maximally tolerated dose of erlotinib when administered in combination with a standard dose of gemcitabine. The secondary objective was to evaluate the preliminary antineoplastic activity of erlotinib administered in combination with gemcitabine in patients with unresectable advanced or metastatic pancreatic cancer, as measured by objective response rate, progression-free survival and estimated median survival. This phase I study served as the platform for development of a regimen for a randomized phase III study in advanced or metastatic pancreatic cancer [16].

Patients and methods

Patient selection

The eligible patients included: male and female patients, aged ≥18 years, documented diagnosis of locally advanced or metastatic pancreatic adenocarcinoma or another epithelial malignancy, gemcitabine-naïve, no restriction on prior number of other chemotherapy regimens, performance status ≥70% by Karnofsky scale, absolute neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, bilirubin ≤2 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2 times the upper limit of normal (ULN) for the institution (5 times if due to hepatic metastases), serum albumin ≥2.5 g/dl, creatinine ≤1.5 times the ULN or creatinine clearance ≥60 ml/min. Exclusions included presence of any other significant and active mental or physical disorder, wide field radiation to ≥25% of marrow bearing bone, more than six cycles with alkylating chemotherapy agent; any prior chemotherapy, hormonal therapy, major surgery or radiation therapy within less than 28 days from planned study treatment. Once the recommended phase II dose levels was established, only patients with pancreatic cancer were enrolled at that dose.

Clinical study design

All patients received gemcitabine 1,000 mg/m^2, intravenously, over 30 min, beginning on day 1, once a week for seven consecutive weeks during the first cycle, then every 3 out of 4 weeks in subsequent cycles. Erlotinib (OSI-774) was supplied by OSI Pharmaceuticals Inc., Melville, NY, USA, in tablets of the hydrochloride salt containing 100, 50 or 35 mg of erlotinib. Two erlotinib doses were tested in this trial: 100 and 150 mg/day, orally, starting on day 3 and continued daily. Initially three patients were entered at the 100 mg/day dose level and the dose was to be escalated to 150 mg/day if no dose limiting toxicities (DLTs) were observed.

Dose limiting toxicity was defined as: (1) grade 4 neutropenia of ≥5 days, or grade 3 or 4 neutropenia associated with fever, (2) grade 4 thrombocytopenia, (3) grade 3 or greater non-hematological drug-related toxicity with the exception of alopecia, grade 3 rash, and other grade 3 limited or medically controlled toxicities such as fever without neutropenia, nausea, vomiting, diarrhea or fatigue, (4) inability due to drug-related toxicity to complete 4 weeks of treatment or requiring more than 7-day delay in treatment due to toxicity. The maximum tolerated dose was defined as the dose preceding the dose at which more than one third of patients experienced DLTs. In the case of DLT, the patient was discontinued from study, while in case of non-DLT, the treatment with dose reduction was allowed.

Study flow

As grade 3 transaminase elevations (DLT) were observed in Cohort IA (100 mg/day of erlotinib), this cohort was first expanded (a total of nine patients treated) and then closed due to overall increased incidence of transaminases elevations (>33%). Subsequently, the investigators agreed to amend the protocol to modify patient eligibility criteria (Cohorts

IB and IIB). The amended eligibility criteria used for Cohorts IB (100 mg/day of erlotinib) and IIB (150 mg/day of erlotinib) included: no more than one prior chemotherapy regimen for metastatic or recurrent malignancy, Karnofsky performance status ≥80%; transaminases (AST and ALT) <1.5 × ULN for the institution; bilirubin within the ULN. Based on new eligibility criteria, three patients were enrolled and treated with 100 mg/day of erlotinib and no additional DLTs were observed. Subsequently, the dose of erlotinib was escalated to 150 mg/day and a total of 14 additional patients were treated at this dose.

Treatment assessments

Baseline assessments included medical history and physical exam including ophthalmological and skin exams, performance status, CBC with differential and platelet count, serum chemistries, urine analysis, pregnancy test in women of child bearing age, 12-lead ECG, diagnostic tumor imaging and tumor markers where clinically indicated. Toxicity assessment was based on National Cancer Institute Common Terminology Criteria, version 2. Tumor responses were assessed using RECIST criteria [17].

Pharmacokinetic studies

Gemcitabine, erlotinib and its major metabolite, OSI-420 were measured in patient plasma using validated methods by a contract laboratory (MDS Pharma Services, St Laurent, QC, Canada). For erlotinib (OSI-774 and OSI-420) pharmacokinetics plasma was collected in cycle 1 on day 3 prior to erlotinib dosing, 15 and 30 min after and 1, 2, 4, 6 and 8 h later; on day 8 prior to gemcitabine and erlotinib dosing and 15 and 30 min and 1, 2, 4, 6 and 8 h later; and on days 9 and 10 and day 15 (prior to gemcitabine and erlotinib dosing). 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 HPLC followed by mass spectrometric single-reaction monitoring. The lower limit of quantitation was 1.1 and 1.0 ng/ml for erlotinib and OSI-420, respectively. It should be noted that a second O-demethylated metabolite, OSI-413, a positional isomer of OSI-420 may also be produced, is not chromatographically separated nor can it be distinguished from OSI-420 by mass spectrometry methods. However, in a ^{14}C-labeled clinical mass balance study with erlotinib, OSI-420 was found to be predominant circulating metabolite, with only minor amounts of OSI-413 detected [18]. For gemcitabine pharmacokinetics individual blood specimens (2 ml) were collected on days 1 and 8 during the first cycle prior to and at the end of infusion, at 15, 30, 60, 240, 360 min after and 24 and 48 h after infusion. Briefly, aliquots of the thawed samples were mixed with an internal standard solution and 1% acetic acid, followed by solid-phase extraction utilizing cation exchange to extract the analytes from the sample matrix. The cartridges were loaded with the samples and washed with water and methanol. The analytes and the internal standard were eluted with 1% ammonium hydroxide in methanol, and the solvent was evaporated to dryness. After reconstitution in mobile phase, an aliquot was analyzed using reverse-phase HPLC followed by mass spectrometric single-reaction monitoring. The lower limit of quantitation for gemcitabine was 10 ng/ml.

Pharmacokinetic parameters for gemcitabine, erlotinib and OSI-420 were analyzed using non-compartmental methods using WinNonlin Enterprise version 4.1.0048 (Pharsight Corporation, Mountain View, CA, USA), based on actual sample times. For gemcitabine (days 1 and 8 data), these parameters included C_{max}, T_{max}, $C_{24\,h}$, $AUC_{0-infinity}$ and $T_{1/2\lambda z}$. The terminal rate constant, λz, was calculated using (at least) the last three quantifiable time points in each plasma profile. $AUC_{0-infinity}$ was calculated using the linear trapezoidal rule and extrapolated to infinity using the relationship: AUC extrapolated = $C_{last}/\lambda z$. For erlotinib and OSI-420 (day 8 data), these parameters were calculated assuming steady state and included C_{max}, T_{max}, $C_{24\,h}$ and AUC_{0-tau}. AUC_{0-tau} for erlotinib was calculated using the log-linear trapezoidal rule.

Pharmacodynamic analyses

Because elevated liver transaminase levels have been observed early in the study (Cohort IA), Spearman correlation analyses were conducted between measures of patient erlotinib and gemcitabine exposure (AUC and C_{max}) and the worst reported toxicity grades for ALT, AST, alkaline phosphatase, total bilirubin, total serum protein, baseline alpha-acid glycoprotein, skin rash and diarrhea. This is because erlotinib is known to be highly bound to AAG in plasma.

Alpha-1 acid glycoprotein samples were sent to Clinical Reference Laboratory Inc., Lenexa, KS, USA, for analysis. Samples were analyzed using a validated turbidimetry assay with a limit of quantitation of 0.1 g/l. Plasma samples were also obtained from each patient for determination of AAG concentrations at baseline and during cycle 1 on days 3, 8, 9, 10 and 15.

Statistical analyses for PK and PD

Two-way ANOVAs were performed to compare erlotinib AUC_{0-tau} and C_{max} between the historical study [26], in which patients received single-agent erlotinib, and this study, in which patients received erlotinib in combination with gemcitabine. Only patients who received 100 or 150 mg doses of erlotinib were included in the analyses. Analyses were conducted on dose-normalized AUC_{0-tau} and C_{max} on the logarithmic (base 10) scale.

One-sample (paired) *t*-tests were performed to compare gemcitabine dose-normalized C_{max} and $AUC_{0-infinity}$ between week 1 (gemcitabine without erlotinib) and week 2 (gemcitabine with erlotinib). Analyses were conducted on the logarithmic (base 10) scale.

Spearman correlation analyses were conducted between measures of patient erlotinib and gemcitabine exposure (AUC and C_{max}) and the worst reported values for ALT, AST, alkaline phosphatase, total bilirubin, total serum protein and baseline AAG.

Results

Patient characteristics

Twenty-six patients received at least one course of erlotinib plus gemcitabine and were evaluable for toxicity. The median age of patients was 63 years, the male to female ratio was 1.0 and the median Karnofsky scale status was 90%. Baseline characteristics are summarized in Table 1.

The disease sites were pancreas ($n = 15$), lung ($n = 2$), breast ($n = 2$) and one patient each with gastric, thyroid, prostate, bladder, renal cell, cholangiocarcinoma and colon cancer.

The median number of cycles on study treatment was 2 (range 1–11). Sixteen patients came off study due to disease progression, four due to treatment-related toxicities, three due to development of inter-current unrelated illness and three patients withdrew consent for non-study related reasons.

Table 1 Baseline patient characteristics ($n = 26$)

Females/males	13/13
Median age, years (range)	63 (29–82)
Tumor type	
Pancreas	15
Breast	2
Lung	2
Other[a]	7
Erlotinib dose levels	
100 mg/day	12
150 mg/day	14
Median KPS (range in percent)	90 (80–100)

[a] Other tumor types included prostate, bladder, renal, thyroid, bile duct, gastric and colon cancer (one of each)

Toxicity

Non-hematological toxicities

The most common non-hematological toxicity was skin rash (Table 2). Eighteen patients (69%) experienced skin rash which was mild and manageable, with no grade 3 or 4 events. The second most common event was diarrhea, which was reported in 14 patients (54%). There were three events of grade 3 diarrhea, all medically controllable. Nausea occurred in 11 patients (42%), and was grade 3 in only 1 patient. Eight patients developed vomiting, but in all cases it was easily manageable. Fatigue was also common, occurring in 14 (54%) patients, and it was grade 3 in 4 patients. Liver toxicity, mainly in the form of ALT or AST elevation occurred in 11 and 10 patients, respectively (42/38%). There were three events of possibly drug-related grade 3 transaminase elevations (ALT/AST) observed in patients in Cohort IA. The median time to transaminase elevation was 30 days ($n = 3$, range 19–125). Two of the three patients that developed transaminase elevations had documented liver metastases. Also, two out of three patients had greater than or equal to four prior chemotherapy regimens. After analyzing these events, it was decided to amend the protocol to incorporate more stringent eligibility criteria for patient enrollment (Cohorts IB and IIB). No additional events of grade 3 or 4 transaminase elevations were reported and the Cohort IIB was then expanded to include additional chemotherapy-naïve patients with pancreatic cancer. No grade 3 or 4 ophthalmological toxicity was observed in this study. One patient developed grade 2 dry-eye syndrome.

Hematological toxicity

Hematological toxicity was mild and has not resulted in dose limiting events (Table 3). Seven patients (27%) experienced anemia. It was grade 1 in three and grade 2 in four cases. A total of four patients (15%) developed grade 3 neutropenia. The median time to nadir was 26 days (range 6–41) and a median time to recovery was 33 days (range 7–48). There were no episodes of grade 4 neutropenia or febrile neutropenia. Two patients (8%) had thrombocytopenia, one was grade 3, with a nadir at day 13.

Table 2 Treatment emergent non-hematological adverse events, highest grade per patient

	Grade	Skin rash	Diarrhea	Nausea	Vomiting	Fatigue	ALT	AST	Bilirubin
Cohort I ($n = 9$) 100 mg	1/2	2/3	3/1	2/1	2/0	2/1	1/1	1/1	0
	3/4	0	0	0	0	0	2/0	2/0	0
Cohort IB[a] ($n = 3$) 100 mg	1/2	2/1	1/0	0/1	1/0	0/1	0	0	0
	3/4	0	0	0	0	0	0	0	0
Cohort IIB[a] ($n = 14$) 150 mg	1/2	4/6	4/2	3/3	2/3	2/4	4/2	4/2	1/0
	3/4	0	3/0	1/0	0	4/0	1/0	0	0

[a] Cohorts IB and IIB include patients that were enrolled according to stricter eligibility criteria

Table 3 Treatment emergent hematological adverse events, highest grade per patient

	Grade	Anemia	Leukopenia	Neutropenia	Thrombocytopenia
Cohort I ($n = 9$) 100 mg	1/2	1/0	0	0	0
	3/4	0	0	2/0	0
Cohort IB[a] ($n = 3$) 100 mg	1/2	0/1	0	0	0
	3/4	0	0	0	0
Cohort IIB[a] ($n = 14$)	1/2	2/3	0/1	0	0/1
150 mg	3/4	0	1/0	2/0	1/0

[a] Cohorts IB and IIB include patients that were enrolled according to stricter eligibility criteria

Deaths

There were five patient deaths that occurred within 30 days of last study treatment. In four cases, deaths were due to disease progression and not considered to be drug related. One case, a fatal episode of pulmonary toxicity, was considered as treatment-related.

Pulmonary toxicity

The fatal episode of pulmonary toxicity occurred in a patient with a non-small cell lung cancer, who was previously treated with chemoradiation. The patient developed acute respiratory failure seven days after his first dosing with gemcitabine and erlotinib (100 mg/day). The patient died from refractory adult respiratory distress syndrome. No post-mortem autopsy was obtained due to patient and family wishes. The event was consistent with erlotinib- or gemcitabine-induced pneumonitis. The second event of respiratory distress occurred in a patient with pancreatic cancer during his fifth cycle of therapy (150 mg/day of erlotinib). He was found to have an endobronchial mass/growth of unknown etiology and developed hemopthysis after diagnostic bronchoscopy. The patient received blood and fresh frozen plasma transfusions, after which, he progressed to develop pulmonary edema. In this case, the pulmonary edema was initially attributed to lung post-transfusion injury, but the relation to study treatment could not be excluded.

Pharmacokinetic results

There were no significant effects of erlotinib administration on the pharmacokinetics of gemcitabine. Comparison of gemcitabine log C_{max} and log $AUC_{0-infinity}$ on days 1 and 8 by paired t-tests gave $P = 0.2991$ and 0.1545, respectively, as shown in Fig. 1.

The results of a two-way ANOVA comparing erlotinib day 8 AUC_{0-tau} and C_{max} between this study and those from a single-agent phase I study of erlotinib showed no significant effects on AUC_{0-tau} or C_{max} ($P = 0.6096$ and 0.7342, respectively), as shown in Fig. 2.

Pharmacodynamic evaluations

A significant correlation (Spearman correlation $r = 0.5742$, $P = 0.0200$) was observed only for erlotinib C_{max} and baseline AAG plasma level. No significant correlation was found for other examined covariates, suggesting no apparent relationship between erlotinib exposure (AUC) and abnormal laboratory values for transaminases, alkaline phosphatase, total protein, bilirubin or skin rash and diarrhea (Table 4).

Antitumor activity

Objective responses

There were two partial responses, one in a patient with cholangiocarcinoma and one in a patient with pancreatic

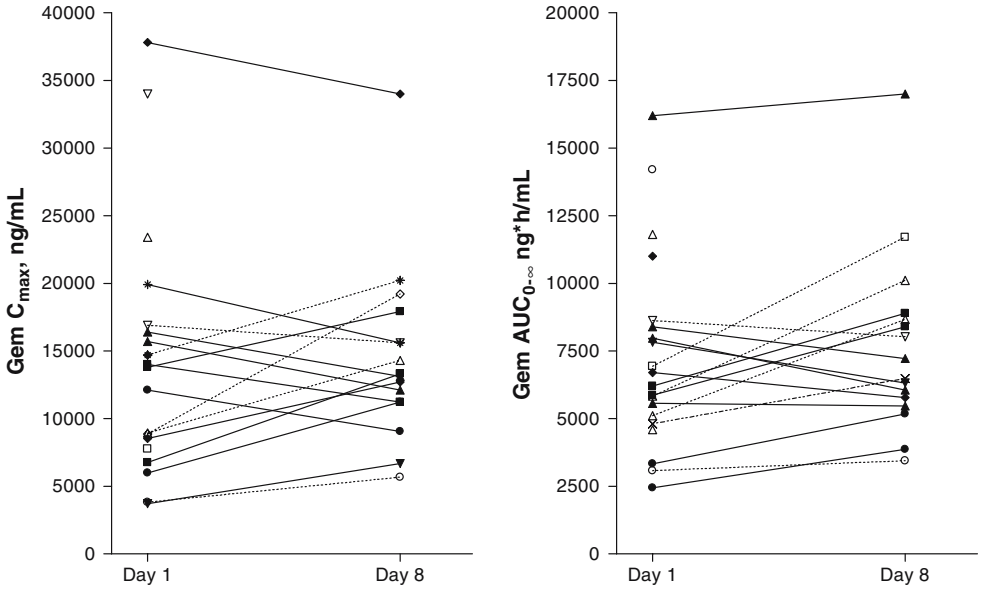

Fig. 1 Gemcitabine C_{max} and $AUC_{0-infinity}$ in plasma, prior to (day 1) and following daily oral doses of erlotinib (day 8). *Open symbols* with *dashed lines*: 100 mg erlotinib; *closed symbols* with *solid lines*: 150 mg erlotinib

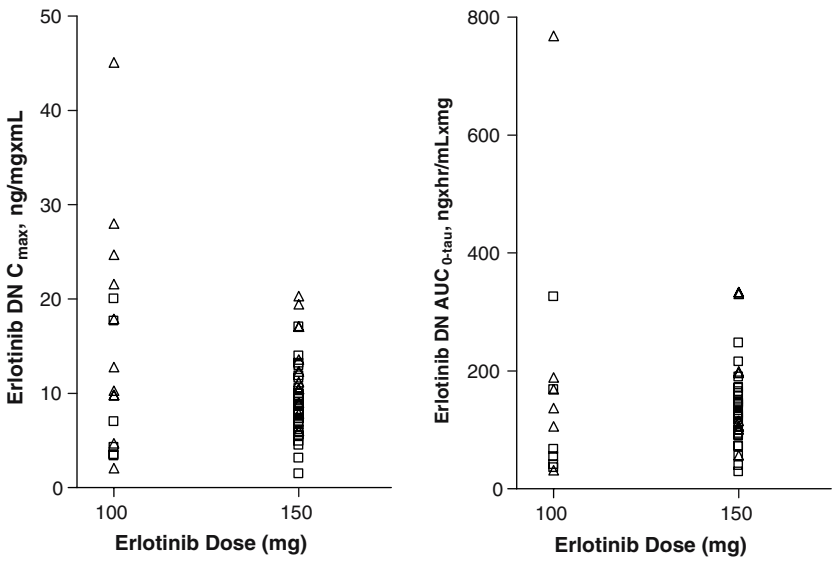

Fig. 2 Comparison of erlotinib dose-normalized C_{max} and AUC from this study (*triangles*) with erlotinib historical monotherapy data (*squares*) [26]

cancer. In the patient with cholangiocarcinoma, the response lasted 17 weeks and in the patient with pancreatic carcinoma the response lasted 31 weeks. Both patients were gemcitabine-naïve.

Activity in pancreatic cancer patients

A total of 15 patients with pancreatic cancer were enrolled of whom 10 had metastatic disease and 5 had locally advanced disease. Of the 12 patients that were evaluable for response, 1 had a partial response (8%), 9 had stable disease for more than 3 months (75%) and 7 of those with stable disease remained on study for 6 months or longer. Eight out of ten non-progressors (including patient with PR) had metastatic disease, two had locally advanced cancer. The progression-free survival for patients with pancreatic cancer ($n = 15$) was 289 days (range 20–351); estimated overall survival was 389 days (range 50–508) and 1-year survival rate was 51%.

Discussion

The EGFR is considered an important therapeutic target in pancreatic cancer; however, the potential mechanisms

Table 4 Correlation analyses (*P* values) of erlotinib and gemcitabine plasma pharmacokinetic parameters with selected biochemistry laboratory parameters

Parameter (worst event)	Erlotinib C_{max}	Erlotinib AUC_{0-tau}	Gemcitabine C_{max} (day 1)	Gemcitabine $AUC_{0-infinity}$ (day 1)
ALT	0.9074	0.5931	0.2767	0.4015
AST	0.5171	0.9821	0.1371	0.1952
Alkaline phosphatase	0.4355	0.9607	0.1503	0.1582
Total bilirubin	0.8733	0.8047	0.0615	0.1664
Total serum protein	0.1497	0.0967	0.8200	0.8521
AAG[a] (baseline)	0.0200 ($r = 0.5742$)[b]	0.0894	0.0587	0.0620
Worst grade any rash	0.1529	0.0933	0.2096	0.2710
Worst grade any diarrhea	0.1140	0.1850	0.7265	0.8396
Worst grade any AE	0.5539	0.4072	0.5145	0.3468

A significant correlation (Spearman correlation $r = 0.5742$, $P = 0.0200$) was observed between erlotinib C_{max} and baseline AAG plasma level, but not for other potential covariates, suggesting no apparent relationship between erlotinib exposure and abnormal laboratory values, skin rash or diarrhea

[a] Alpha-acid glycoprotein

[b] Spearman correlation coefficient

of EGFR pathway disregulation in pancreatic cancer are not well understood [19, 20]. A phase II study of the anti-EGFR monoclonal antibody cetuximab plus gemcitabine in patients with unresectable pancreatic cancer demonstrated favorable tolerability and efficacy [11]. More recently, another study using a different humanized anti-EGFR monoclonal antibody in combination with gemcitabine also demonstrated promising activity [21]. Our study was the first involving a combination of an EGFR kinase tyrosine inhibitor erlotinib and gemcitabine. This study was a pilot for a larger phase III randomized trial for patients with advanced or metastatic pancreatic cancer [16]. In addition to pancreatic cancer, the gemcitabine plus erlotinib combination is of interest in other gemcitabine-sensitive epithelial malignancies including lung, breast and urinary bladder carcinomas.

In general, the toxicity profile was favorable and known erlotinib-related toxicities such as skin rash and diarrhea were mild and manageable. In the first cohort of patients (Cohort IA), treated with 100 mg/day of erlotinib, we have encountered an apparent increase in the incidence of transaminase elevations. However, when stricter inclusion criteria were adopted, restricting the number of prior chemotherapy regimens, performance status and liver function tests, we were able to administer the full dose of 150 mg/day without increased incidence of hepatotoxicity. It is important to consider that gemcitabine alone can induce transaminase elevations in some patients [22]. We have encountered two events of pulmonary toxicity on this study. At least one, a case of acute respiratory failure in a patient with lung cancer, was felt to be related to erlotinib, gemcitabine or the combination. Similar cases of interstitial pneumonitis have been reported in lung cancer patients treated with either erlotinib or gefitinib [23, 24]. The reported incidence was about 2% in Japan and <1% in US series. The reported incidence of gemcitabine-induced pneumonitis is <1% and it is more common in patients who received prior thoracic radiation therapy [25]. Due to the small study sample, it is difficult to ascertain whether the addition of erlotinib to gemcitabine may further increase the incidence of this rare but serious event.

The pharmacokinetic analyses in this study do not indicate any significant interactions between erlotinib and gemcitabine and the AUC and C_{max} are comparable to those observed in historic controls where patients received erlotinib only [26].

We have seen some preliminary evidence of antitumor activity. One patient with pancreatic cancer had a partial response and several patients achieved prolonged disease stabilization. More importantly, the estimated overall survival was 389 days and 1-year survival rate of 51% for 15 pancreatic cancer patients enrolled in this trial. Although we should be cautious in interpreting this data, it is encouraging and supports further investigation of erlotinib/gemcitabine combination in patients with pancreatic carcinoma. It is important to consider that patients were not selected on the basis of intratumoral EGFR expression or any other biological marker. In lung cancer patients, those with tumors carrying an EGFR gene mutation and/or amplification had a higher chance of response or benefit to EGFR blockade [27, 28]. It is not yet known if similar EGFR gene alterations are present in pancreatic tumors.

NCI Canada has recently completed a large phase III trial where patients were randomized to gemcitabine vs. gemcitabine plus erlotinib [16]. Due to safety

concerns, the starting erlotinib dose for this study was 100 mg/day. Because of the rapid study accrual, only 48 patients received a full dose of 150 mg/day of erlotinib, after it was established to be safe. Modest but statistically significant improvement in median (6.4 months vs. 5.9 months), overall (25% improvement) and 1-year survival (21% vs. 17%) was reported, which recently led to the FDA approval of erlotinib in combination with gemcitabine. Clearly, in our study, we have shown that selected patients with advanced pancreatic cancer (KPS $\geq$80%, AST/ALT $\leq$1.5 $\times$ ULN and bilirubin $\leq$ ULN) can tolerate full dose of erlotinib at 150 mg/day, administered in combination with gemcitabine. One may hypothesize that the benefit seen in a phase III study could have been optimized if the higher dose of erlotinib was attempted in most patients [16]. Further investigations are warranted in order to select patients with higher chance of response and to better define optimal schedule/sequence of erlotinib when given alone or in combination, to patients with pancreatic cancer.

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