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ORIGINAL ARTICLE

# An open-label study to describe pharmacokinetic parameters of erlotinib in patients with advanced solid tumors with adequate and moderately impaired hepatic function

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**Abstract**
*Purpose* To compare the pharmacokinetic (PK) parameters of a single dose of erlotinib in cancer patients with moderate hepatic impairment (MHI) to those of cancer patients with adequate hepatic function (AHF).
*Methods* Cancer patients with either AHF or MHI were treated with a single 150 mg dose of erlotinib on day 1 only followed by 96 h of plasma sampling for PK assessment. From day 5, patients were allowed to continue daily erlotinib in a maintenance phase. Non-smoking patients were stratified into an AHF cohort (total bilirubin $\leq$ upper limit of normal [ULN] and ALT/AST $\leq$ 1.5 X ULN) or a MHI cohort (Child-Pugh score of 7–9). The frequency of adverse events and laboratory changes were assessed.
*Results* Thirty-six patients, 21 with AHF and 15 with MHI, received at least one dose of erlotinib. The PK of erlotinib was similar between the two cohorts with a median $C_{max}$ of 1.09 versus 0.828 μg/mL and corresponding median $AUC_{0-t}$ 29.3 versus 30.5 μg h/mL for the AHF and MHI cohorts, respectively. Adverse events from erlotinib in cancer patients with MHI were consistent with the known safety profile.
*Conclusions* The PK and safety profiles of erlotinib in patients with MHI were similar to those with AHF. As a result, a reduced starting dose of erlotinib in patients with MHI is not required and treatment should be guided by patients' tolerability.

**Keywords** Erlotinib · Hepatic function · Pharmacokinetics · Protein binding · Safety

**Abbreviations**
AHF Adequate hepatic function
MHI Moderate hepatic impairment

## Introduction

Erlotinib is an oral antitumor agent that inhibits the epidermal growth factor receptor (EGFR) resulting in inhibition of cell proliferation, invasion, metastasis and tumor-induced angiogenesis as well as a potential increase in the antitumor efficacy of chemo- and radiotherapy [1]. Erlotinib is currently approved as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen, as maintenance treatment of patients

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**Table 1** Criteria for hepatic function cohort determination

| MHI | | | | AHF |
|---|---|---|---|---|
| Child-Pugh score 7–9 | | | | Total bilirubin ≤ ULN |
| Points scored for observed findings | | | | AST/ALT ≤ 1.5 X ULN |
| | 1 | 2 | 3 | |
| Encephalopathy[a] | None (0) | 1 or 2 | 3 or 4 | |
| Ascites | Absent | Slight | Moderate | |
| Serum bilirubin (mg/dL) | <2 | 2–3 | >3 | |
| Serum albumin (g/dL) | >3.5 | 2.8–3.5 | <2.8 | |
| Prothrombin time (sec prolonged) | <4 | 4–6 | >6 | |

*MHI* moderate hepatic impairment, *AHF* adequate hepatic function

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity

with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line therapy and in combination with gemcitabine for initial treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer [2, 3].

Erlotinib is well absorbed (60%) after oral administration, and bioavailability is approximately 100% when given with food. Peak plasma levels occur around 4 h postdose, and the median elimination half-life is 36 h. The drug is highly protein bound (approximately 93%) to albumin and alpha-1-acid glycoprotein (AAG). Erlotinib is primarily metabolized in the liver by cytochrome P450 (CYP) 3A4 and to a lesser extent CYP1A2. It is excreted predominantly via the bile, with less than 10% being recovered in the urine [4, 5]. Total bilirubin, AAG and smoking status are noted factors that affect clearance. However, population pharmacokinetic (PK) studies to date have revealed no significant relationships of clearance to these or other covariates [4–7].

For drugs primarily metabolized by the liver, the FDA recommends conducting a PK study in patients with hepatic impairment as determined by Child-Pugh classification to determine whether the organ dysfunction has an affect on exposure of the drug [8]. Registration trials for erlotinib were restricted to patients with adequate renal and hepatic function [2, 3, 9, 10]. Therefore, this study was conducted to compare the PK parameters of a single 150 mg dose of erlotinib in cancer patients with moderate hepatic impairment (MHI) to those with adequate hepatic function (AHF); evaluate the safety of this dose; and evaluate erlotinib protein binding in cancer patients with MHI.

## Materials and methods

### Patient selection

Eligible patients included non-smokers with histologically or cytologically confirmed advanced solid malignancies potentially responsive to erlotinib or for whom no effective therapy existed. Patients were enrolled into two cohorts according to hepatic function: AHF (total bilirubin ≤ ULN, AST/ALT ≤ 1.5 X ULN) and MHI (Child-Pugh score of 7–9) [11] (Table 1). Other relevant eligibility criteria included: Eastern Cooperative Oncology Group performance status (PS) of 0–2; adequate hematopoietic function and renal function; expected remaining life span ≥3 months; no encephalopathy ≥ grade 2; and no CYP3A4 or CYP1A2 inhibitor/inducer or warfarin-derivative anticoagulant within 14 days of day 1 and until after last PK sample on day 5. The use of tobacco or nicotine-containing products within 1 month or during the study was not allowed. Patients with gastrointestinal abnormalities affecting the absorption of erlotinib were excluded. Informed consent was obtained according to federal/international and institutional guidelines. The study was approved by the Institutional Review Board or Ethics Committee at each site. (ClinicalTrials.gov Identifier: NCT00139620; IND #53,728).

### Study design and drug administration

This was a multi-center, open-label, 2-arm study comparing erlotinib exposure in cancer patients with AHF and MHI. Patients were enrolled at 5 different institutions.

All patients received a single 150 mg dose of erlotinib on day 1 followed by 96 h of PK sampling. Following the final plasma PK sample on day 5, patients entered a continuous daily dosing maintenance phase until disease progression or unacceptable toxicity. A sample size of 21 patients in each cohort, with a total population of 42 patients, was planned to allow for the estimation of the ratio of geometric means with 90% confidence intervals of ±35% for key PK parameters, assuming a conservative interpatient standard deviation for AUC and $C_{max}$ of 0.337 determined from a previous trial [12]. Adverse events and laboratory data were summarized descriptively. Efficacy endpoints were not evaluated.

Patients continuing on erlotinib therapy started at a dose of erlotinib 150 mg/day, with possible dose reductions to 100 and 50 mg/day for toxicity if necessary. Erlotinib was reduced by one dose level for any grade 3 toxicity and was discontinued for any grade 4 toxicity. Additionally, if a patient experienced interstitial lung disease of any severity, erlotinib was discontinued. Toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0.

Erlotinib tablets were supplied by OSI Pharmaceuticals, Inc (Boulder, CO). Erlotinib was taken orally once daily with up to 200 mL of water, at least 1 h before or 2 h after meals or medications.

### Pretreatment and follow-up studies

Clinical laboratory tests and Child-Pugh scoring were performed at screening and again within 24 h of the day 1 dose to confirm eligibility. Laboratory studies included a complete blood count (CBC) with platelets and hemoglobin, a liver panel (including albumin, alkaline phosphatase, total bilirubin, ALT and AST), blood urea nitrogen, creatinine and prothrombin time. Smoking status was confirmed by cotinine test at baseline. On day 5, all laboratory studies completed on day 1 were repeated with the exception of the CBC. Treatment-emergent adverse event (new or worsened from baseline) evaluations occurred on day 1, day 5, weekly for the first 4 weeks and every 3–4 weeks until study discontinuation. Adverse events were graded according to the NCI CTCAE v3.0. Disease assessment was conducted per institutional practice.

### Pharmacokinetic and protein binding sampling and assay

For the determination of PK parameters, whole blood samples were obtained by venipuncture at designated time intervals. Samples were collected on days 1–5 according to the following schedule: 15 min prior to erlotinib dosing and then 1, 2, 4, 6, 8, 10, 24, 30 48, 72 and 96 h after dosing on day 1. The 96 h sample was drawn prior to starting continuous erlotinib dosing in the maintenance phase. Three to five mL of blood was collected at each time point and centrifuged within 30 min of collection for 15 min, at 3,000 rpm and 5°C. Plasma was removed from the cell fraction and frozen at −20°C or below until analysis.

Plasma was assayed for erlotinib and its major metabolite OSI-420 with liquid chromatographic/tandem mass spectrometry (HPLC/MS–MS). The analytic method for the determination of erlotinib and OSI-420 in human plasma was developed and validated at OSI Pharmaceuticals and has been previously published [7]. The lower limit of quantitation for both analytes was 1 ng/mL.

Non-compartmental analysis was used to determine the PK parameters for erlotinib and OSI-420 using WinNonlin 5.2 (Pharsight Corporation, Mountain View, CA). Pharmacokinetic parameters used to measure a PK effect due to hepatic impairment were summarized using descriptive statistics and geometric means using SAS, v9.1.3 statistical software program (SAS Institute, Cary, NC).

Plasma samples collected on day 1 at the 4 h postdose time point were also used to determine plasma protein binding. If plasma samples from the 4 h time point were not available or insufficient, the 2 or 6 h postdose plasma samples were utilized. The percentage of erlotinib bound to plasma proteins was determined by an ultracentrifugation method at OSI Pharmaceuticals (Boulder, CO). Aliquots of 200 μL were transferred into a Beckman clear centrifugation tube in triplicate. Centrifugation was carried out in a Beckman L-80 Ultracentrifuge (Beckman Coulter, Inc., Fullerton, CA) in a 42.2 Ti centrifuge head at 20°C for 4 h at 35,000 revolutions per minute. Twenty microliter aliquots were collected from just below the surface on the centrifuged samples and moved to a fresh microcentrifuge tube containing 180 μL of blank human plasma, then was mixed and frozen at −20°C. Erlotinib concentrations were determined by HPLC/MS–MS. A dilution factor of 10 was used to calculate the final unbound concentrations of erlotinib. The percent erlotinib bound was calculated using the formula: (1—median unbound erlotinib/total erlotinib) × 100. A non-evaluable patient was determined as one that had ≥2 values BLOQ of 10 ng/mL unbound erlotinib concentrations. Plasma samples for the determination of AAG were analyzed by Clinical Reference Laboratory, Inc. (Lenexa, KS, US) using a validated turbidimetric assay (limit of quantitation 0.1 g/L) [12].

## Results

### Patient demographics

Thirty-nine patients, 21 with AHF and 18 with MHI, were enrolled into the study. Fifteen of the 18 MHI patients initiated therapy. Thirty-six patients (21 with AHF and 15 with MHI) completed the PK assessments and were included in

**Table 2** Patient demographics

| | MHI | AHF |
|---|---|---|
| No. of patients | 18 | 21 |
| Sex, male/female | 15/3 | 12/9 |
| Age, years | | |
| Median | 57 | 63 |
| Range | 31–70 | 40–85 |
| Race | | |
| White | 14 | 20 |
| Black | 4 | – |
| Asian | – | 1 |
| ECOG performance status | | |
| 0 | – | 10 |
| 1 | 14 | 10 |
| 2 | 4 | 1 |
| Previous treatment | | |
| Chemotherapy | | |
| 0–1 regimens | 8 | 6 |
| 2–5 regimens | 7 | 7 |
| >5 | 3 | 8 |
| Disease-related surgery | 7 | 17 |
| Radiation | 6 | 11 |
| Hormonal, immuno- or cytostatic therapy | 1 | 3 |
| Tumor type | | |
| Hepatocellular | 6 | 1 |
| Non-small cell lung | – | 4 |
| Pancreatic | 1 | – |
| Cholangiocarcinoma | 3 | 1 |
| Colorectal | 3 | 5 |
| Esophageal | 1 | 3 |
| Other[a] | 4 | 7 |

*MHI* moderate hepatic impairment, *AHF* adequate hepatic function

[a] Includes melanoma (2 patients), breast, clear cell sarcoma, thyroid, ovarian, head and neck, endometrial adenocarcinoma, vaginal squamous cell, gastric and undetermined carcinoma, either cholangio or pancreatic in nature

the safety evaluation. Thirty-five of the 36 patients continued to receive erlotinib during the maintenance phase of the study. Patient characteristics are listed in Table 2. The median Child-Pugh score in the MHI cohort ($N = 18$) was 8.5 (range 7–11). Two patients in this cohort had a Child-Pugh score of $\geq$10 and did not receive study drug. One patient with a score of 10 had ascites that was initially scored incorrectly and received erlotinib before the error was found. There were a higher percentage of patients with a PS of 2, males, black patients and younger patients in the MHI cohort. Additionally, a higher frequency of severe baseline signs and symptoms was seen in this cohort, and 47% had grade 3 or 4 elevated bilirubin. Eight of the patients (53%) with MHI had hepatobiliary cancers compared with 2 patients (10%) with AHF. Sixty-two percent of the patients were former smokers. The median number of days on treatment in the maintenance phase was 31 (range 4–453) in the MHI cohort and 49 (range 7–116) in the AHF cohort.

## Pharmacokinetics and protein binding

Plasma sampling for PK studies was performed on all 36 patients who received at least one dose of erlotinib. Pharmacokinetic parameters of erlotinib and its metabolite, OSI-420, for both treatment cohorts are reported in Table 3. Median plasma concentration–time curves are shown in Fig. 1. Following drug administration, plasma concentrations of erlotinib peaked earlier in patients with AHF as compared to MHI. This trended toward but did not reach statistical significance ($P = 0.06$), although the $T_{max}$ values were highly variable in both cohorts. The percent geometric mean ratios for the $C_{max}$ and $AUC_{0-t}$ of erlotinib were 74 (90% CI: 57.3, 95.6) and 92 (90% CI: 69.1, 123.2), respectively. The median $C_{max}$ of erlotinib was statistically significantly lower in the MHI cohort, which is consistent with the delayed $T_{max}$. As a result, there was no increase in erlotinib exposure in the MHI cohort. Interpatient variability on the PK of erlotinib was higher in the MHI cohort compared to the AHF cohort. The PK of the OSI-420 metabolite was similar in patients across both treatment cohorts.

Serum albumin, AAG concentration and percent plasma protein binding of erlotinib were used to evaluate the effect of MHI on erlotinib protein binding. All evaluable patients in both treatment cohorts had samples collected and albumin and AAG concentrations measured. Only 10 of 15 patients in the MHI cohort had sufficient samples for plasma protein binding studies. As seen in Table 4, the median albumin concentration was lower in the MHI cohort compared to the AHF cohort. However, the median AAG concentrations and median percent plasma protein binding of erlotinib appear to be unaffected by MHI.

## Safety

All patients with the exception of one in the AHF cohort experienced at least one adverse event during the study. Erlotinib-related adverse events were predominantly mild to moderate, and the frequency for all grades of drug-related events was similar between both cohorts (Table 5). The most common erlotinib-related adverse events documented in both cohorts were skin rash, diarrhea, nausea, vomiting and fatigue. More patients in the MHI cohort experienced serious adverse events regardless of causality (73%) than in the AHF cohort (33%). Serious hepatic events were experienced by three patients, all in the MHI cohort: one with grade 2 hepatic failure which was

**Table 3** Pharmacokinetic parameters for erlotinib and OSI-420

| Parameter | MHI ($N = 15$) | AHF ($N = 21$) |
|---|---|---|
| | Median (max–min); SD | |
| Erlotinib | | |
| $C_{max}$ (μg/mL) | 0.828<br>(0.241–2.35); 0.571<br>Geometric mean (90% CI)<br>0.805 (0.608, 1.06) | 1.09<br>(0.6–1.87); 0.298<br>Geometric mean (90% CI)<br>1.09 (0.98, 1.21) |
| $T_{max}$ (h) | 6 (1–24) | 2 (1–24) |
| $AUC_{0-t}$ (μg h/mL) | 30.5<br>(4.68–80.3); 19<br>Geometric mean (90% CI)<br>27.0 (19.9, 36.7) | 29.3<br>(14.9–62.1); 11.2<br>Geometric mean (90% CI)<br>29.3 (25.7, 33.4) |
| *Cl*/*F* (L/h) | 3.92<br>(1.86–31.9); 7.35 | 5.11<br>(1.87–10); 1.99 |
| *T* 1/2*z* (h) | 18<br>(4.7–69.8); 19.6 | 15.2<br>(6.92–53.1); 11.6 |
| *Vz*/*F* (L) | 158<br>(27.3–505); 114 | 111<br>(56.9–224); 44.5 |
| OSI-420 | | |
| $C_{max}$ (μg/mL) | 0.055<br>(0.02–0.3); 0.066<br>Geometric mean (90% CI)<br>0.059 (0.045, 0.079) | 0.073<br>(0.041–0.15); 0.026<br>Geometric mean (90% CI)<br>0.076 (0.067, 0.086) |
| $T_{max}$ (h) | 8 (1–48) | 4 (1–24) |
| $AUC_{0-t}$ (μg h/mL) | 2.47<br>(0.37–13.7); 3.07<br>Geometric mean (90% CI)<br>2.37 (1.7, 3.32) | 1.88<br>(1.2–4.83); 0.846<br>Geometric mean (90% CI)<br>2.00 (1.76, 2.28) |
| *T* 1/2*z* (h) | 20.5<br>(9.88–57.0); 15.6 | 15.1<br>(8.49–51.8); 9.13 |

*MHI* moderate hepatic impairment, *AHF* adequate hepatic function, *SD* standard deviation

deemed drug-related and a grade 4 hepatic encephalopathy determined unrelated to erlotinib; one with grade 4 hepatorenal syndrome; and one with grade 4 hepatic failure both considered unrelated to erlotinib. During the maintenance phase, eight patients required erlotinib dose reduction (6 with AHF, 2 with MHI), all due to rash and diarrhea.

Of the 36 evaluable patients, twenty-six discontinued treatment due to disease progression, 8 versus 18 patients in the MHI and AHF cohorts, respectively. Seven patients, 5 MHI and 2 AHF, stopped treatment due to an adverse event. Two patients in the AHF cohort requested study withdrawal. One patient in the MHI cohort continued erlotinib past database lock. Two deaths due to adverse events occurred in the MHI cohort during the maintenance phase: one patient died from hepatorenal syndrome on day 17 (2 days after last erlotinib dose) and the other died due to worsening liver failure on day 14 (9 days after last erlotinib dose). Neither death was considered related to erlotinib. Eight other patients in the MHI cohort died of progressive disease within 30 days of receiving their last erlotinib dose. There were no deaths in the AHF cohort.

## Discussion

EGFR is a type 1 receptor tyrosine kinase involved in the regulation of cell differentiation and proliferation. Erlotinib plasma concentrations increase proportionally with dose, and single-dose data predict multiple-dose exposure [13]. Since erlotinib is predominantly metabolized by the liver, the objective of this study was to evaluate whether patients with MHI have significantly higher erlotinib exposure and therefore would require a lower erlotinib dose. The study was not intended to evaluate potential hepatotoxicity.

The target sample size of 21 patients in each cohort was not achieved during the 2 years the study was conducted due to slow accrual to the MHI cohort. A preliminary review of the PK data was performed, which indicated that there were no statistical differences between the two cohorts, and review of the sample size calculations concluded that enrollment of additional MHI patients was unlikely to alter study findings. Based on this information, the regulatory authorities in the United States, Canada and Europe deemed the study had fulfilled the postapproval commitment and accepted the smaller sample size in the MHI cohort.

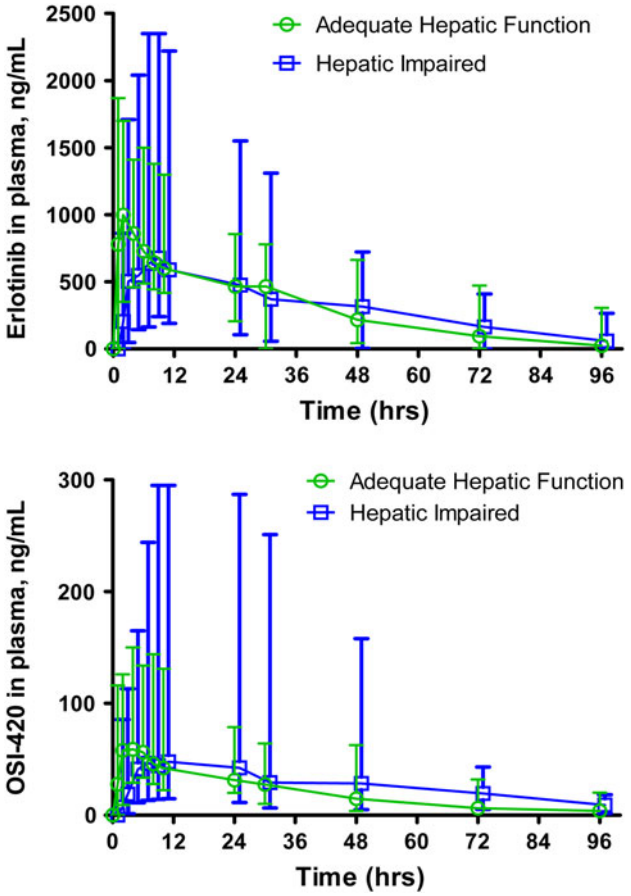


**Fig. 1** Median erlotinib and OSI-420 plasma concentration versus time following a single 150 mg oral dose of erlotinib. *Error bars* denote minimum and maximum values. The *x* axis has been shifted 1 h to the *right* for the hepatic impaired data to show *error bars*

Our results demonstrated that the PK parameters of erlotinib in cancer patients with MHI were similar to cancer patients with AHF. The median $T_{max}$ following oral administration was highly variable between the two cohorts although not statistically significant. While a lower median $C_{max}$ was seen in the MHI cohort, the median $AUC_{0-t}$ values were similar and did not reach statistical significance. Overall, MHI did not result in a significant increase in erlotinib exposure or have any effect on drug plasma protein binding.

The PK and plasma protein binding results in this study are within the values observed in other PK studies assessing erlotinib in cancer patients with sufficient hepatic function [4, 7, 13]. In a CALGB study, Miller et al. also examined the effect of hepatic as well as renal dysfunction on the PK of erlotinib in a phase 1 dose escalation study where patients were stratified into 3 hepatic dysfunction groups based on albumin, AST and direct bilirubin [1, 7]. The Child-Pugh score was assessed for patients in the hepatic cohorts but was not used for classification. Instead, the hepatic dysfunction group included a broad range of bilirubin abnormalities ranging from 1 to 7 mg/dL. The authors concluded that hepatic impaired groups exhibited reduced erlotinib clearance and a longer half-life as compared to the renal dysfunction group. No relationship between direct bilirubin values, Child-Pugh scores or AAG concentrations and the oral clearance of erlotinib was found in the hepatic cohorts. The authors recommended the starting dose of erlotinib for patients with hepatic dysfunction be reduced to 75 mg/day consistent with decreased clearance. However, plasma concentration versus time data were only collected for 24 h following the first dose of erlotinib, which is insufficient for accurate estimation of plasma clearance based on the 36-h erlotinib half-life. Our study utilized the Child-Pugh criteria as required by the FDA. Therefore, there was a wide variation in the extent of organ dysfunction between patients enrolled in the two studies, which could explain the divergent dose recommendations. Additionally, our study enrolled non-smokers after biochemical verification. Cigarette smoking interferes with erlotinib metabolism and may account for the varying PK parameters.

**Table 4** Effect of hepatic dysfunction on serum albumin, plasma AAG and plasma protein binding of erlotinib

| | MHI ($N = 15$) | AHF ($N = 21$) |
|---|---|---|
| | Median (range) | |
| Albumin (g/dL) | 2.9 (1.3–3.5) | 3.5 (2.4–4.4) |
| AAG (mg/dL) | 126 (54–182) | 124 (74–225) |
| Erlotinib % bound | 96.7 (95.6–98.9)[a] | 97.4 (91.4–98.4) |

*MHI* moderate hepatic impairment, *AHF* adequate hepatic function

[a] $N = 10$

Genetic polymorphisms in *CYP3A4/3A5* and *ABCG2* genes have been shown to affect the PK of erlotinib. Variations in these genes are associated with higher AUC and $C_{max}$ levels as well as decreased clearance and potentially contribute to interpatient variability of this drug [14, 15]. Pharmacogenetic assessments were not included in this study, and thus, the exact influence of these polymorphisms on the outcome of the study is not known, however, as previously stated that the PK and protein binding values of erlotinib observed within this study are consistent with those seen in other studies conducted in patients with adequate hepatic function.

Although infrequent, liver function abnormalities have been reported in single agent and combination studies with erlotinib as well as gefitinib, another EGFR inhibitor [3, 16–20]. Generally, these abnormalities have been mild and transient. There have been published case reports of acute severe hepatitis with erlotinib and acute hepatotoxicity with gefitinib, which raises the possibility of whether this is an EGFR tyrosine kinase inhibitor class effect [21–26].

**Table 5** Erlotinib-related adverse events occurring in ≥10% of patients

| | MHI ($N = 15$) | | AHF ($N = 21$) | |
|---|---|---|---|---|
| | Any *n* (%) | 3–4 *n* (%) | Any *n* (%) | 3–4 *n* (%) |
| Skin and subcutaneous tissue disorders | 8 (53) | – | 16 (76) | 3 (14) |
| Dermatitis acneiform | 4 (27) | – | 5 (24) | 2 (10) |
| Rash | 3 (20) | – | 6 (29) | – |
| Pruritus | 1 (7) | – | 5 (24) | – |
| Rash papular | 2 (13) | – | 3 (14) | – |
| GI disorders | 8 (53) | 2 (13) | 14 (67) | 1 (5) |
| Diarrhea | 4 (27) | 2 (13) | 10 (48) | 1 (5) |
| Nausea | 2 (13) | – | 10 (48) | – |
| Vomiting | 3 (20) | – | 3 (14) | – |
| General disorders | 3 (20) | – | 9 (43) | – |
| Fatigue | 3 (20) | – | 9 (43) | 1 (5) |
| Metabolism and nutrition disorders | 2 (13) | – | 7 (33) | – |
| Anorexia | 1 (7) | – | 7 (33) | – |
| Nervous system disorders | 2 (13) | 1 (7) | 4 (19) | – |
| Headache | 1 (7) | – | 3 (14) | – |

*MHI* moderate hepatic impairment, *AHF* adequate hepatic function

Patients enrolled into this study were assigned into one of two cohorts based on their hepatic function. Comparison of erlotinib tolerability between the two cohorts is inappropriate given the inherent differences in the populations, including comorbidities and prognosis. There was no evidence of increased erlotinib toxicity in patients with MHI, considering the significant preexisting comorbidities in this population. The two cohorts assessed in this study differed considerably in demographic and baseline characteristics, and these inherent differences may have played a part in the observed outcomes. Baseline findings likely contributed to the fact that the MHI cohort had more serious and severe adverse events during the study. Overall, 14 patients (39%) experienced grade 3 adverse events, the majority being gastrointestinal related, and 7 patients (19%) experienced grade 4 events (dyspnea, stroke, rectal pain, pulmonary embolism, GI bleed, renal failure, hepatic failure and encephalopathy), none of which were deemed related to erlotinib. More patients in the MHI cohort (87%) experienced severe adverse events than those in the AHF cohort (48%).

Ten of the 15 patients in the MHI cohort died on treatment or within 30 days of last dose. The majority of deaths were attributed to disease progression. Two patients died during the maintenance phase of the study from events deemed unrelated to erlotinib: one patient from hepatorenal syndrome and the other from worsening liver failure.

Six out of the 10 patients in the MHI cohort who died had a baseline total bilirubin > 3 X ULN, which suggests severe rather than MHI. This finding illustrates the limitations of using the Child-Pugh scoring in patients with metastatic cancer in the assessment of hepatic dysfunction as recommended by the FDA for PK studies in patients with hepatic impairment [8]. It is important to note that this scoring system was created to assess surgical risk in patients with cirrhotic end-stage liver disease, and therefore, some of the scoring variables may not be applicable to cancer patients. The NCI Organ Dysfunction Working Group recommends utilizing a classification based on total bilirubin and AST values. In comparing the Working Group classification with the Child-Pugh scoring system, the authors showed that in cancer patients total bilirubin is a major factor in classifying the severity of hepatic dysfunction [27]. The outcomes of the aforementioned study support the findings of our study that patients with elevated baseline total bilirubin (≥3 X ULN) had severe rather than MHI. Additionally, 47% of patients in the MHI cohort had baseline grade 3 and 4 bilirubin elevations, further suggesting that these patients exhibited more severe hepatic dysfunction. Elevated baseline total bilirubin may be an indicator that these patients had some degree of cholestasis. It is unclear how cholestasis affects hepatic drug metabolism. There is currently no data regarding the PK of erlotinib in patients with cholestatic disease.

Based on the PK and safety information attained within this study, the prescribing information for erlotinib has been revised. This information now warns that the use of erlotinib in patients with total bilirubin > 3 X ULN should be used with extra caution and patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B or C) should be closely monitored. Erlotinib dosing should be interrupted or discontinued if changes in liver function are observed such as doubling of total bilirubin and/or tripling of transaminases in the setting of abnormal pretreatment values. Dosing with erlotinib should be interrupted or discontinued if total bilirubin is > 3 X ULN and/or transaminases are greater than 5 X ULN in the setting of normal

pretreatment values. Additionally, hepatorenal syndrome has been added to the warning section under renal failure [4]. At present, no guidelines exist to address the frequency or timing of hepatic monitoring in patients with hepatic impairment receiving erlotinib. It has been suggested that routine monitoring of liver function tests be performed in all patients 2 weeks after initiation of therapy and monthly thereafter [28].

Patients with MHI are tenuous, typically in poor health, and clinical variables used to calculate the Child-Pugh score can change quickly, making eligibility difficult to establish. These issues resulted in slow accrual of patients to the MHI cohort and early study closure. This same difficulty in enrollment was seen with the CALGB study and is characteristic of hepatic dysfunction studies conducted with hepatically metabolized oncology medications [15].

In summary, the results of the PK and protein binding evaluations from this study demonstrate that patients with MHI do not require erlotinib dose reduction at treatment initiation. Overall, the adverse events reported during the study were consistent with those reported in other erlotinib clinical trials. Patient tolerability of erlotinib should be used to determine all subsequent dose modifications. Careful monitoring of patients with hepatic impairment while on erlotinib remains essential and should not be neglected.

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