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ORIGINAL ARTICLE

The effect of different etiologies of hepatic impairment on the pharmacokinetics of gefitinib

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Abstract
Purpose We investigated whether the pharmacokinetics and tolerability of gefitinib were altered in patients with hepatic impairment due to cirrhosis or hepatic metastases in two open, parallel-group, multicenter studies.
Methods In Study 1, subjects with normal hepatic function or mild, moderate, or severe hepatic impairment (Child-Pugh criteria) due to cirrhosis received single-dose gefitinib 250 mg ($n = 10$ per group). In Study 2, patients with solid malignant tumors with normal liver biochemistry ($n = 18$), moderate ($n = 16$), or severe ($n = 7$) hepatic impairment (liver biochemistry tests) due to metastases received gefitinib 250 mg daily for 28 days.
Results In Study 1, the geometric mean area under the plasma concentration–time curve (AUC) for gefitinib was significantly higher in patients with hepatic impairment compared with healthy subjects; hepatic impairment was associated with reduced gefitinib plasma clearance, longer half-life, and reduced plasma metabolite levels. In Study 2, the geometric mean gefitinib steady-state AUC during the 24-h dosing interval was slightly, but not significantly, higher in patients with moderate hepatic impairment; there were, however, no significant differences between groups in gefitinib and metabolite pharmacokinetic parameters. In both studies, gefitinib was well tolerated across all cohorts.
Conclusions We conclude that the effect of hepatic impairment on gefitinib pharmacokinetics depends on the underlying etiology of that impairment and its classification.

Keywords Cirrhosis · Gefitinib · Hepatic impairment · Liver metastases · Pharmacokinetics

Introduction

Hepatic impairment in patients with advanced cancer is most commonly due to liver metastases but may also be a consequence of other liver diseases such as hepatitis, cirrhosis, or chemotherapy-induced toxicity. Pathological changes in the liver may lead to a reduction in hepatic

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blood flow, lower cell permeability, and a decrease in the activity of metabolic enzymes that may result in alterations to the pharmacokinetics of drugs [1, 2]. Such changes could influence the exposure and consequently safety of anticancer agents that undergo hepatic metabolism or elimination such as the anthracyclines [1], vinca alkaloids [1, 3], and taxanes [4–6].

Guidelines produced by the United States Food and Drug Administration (FDA) [7] and the European Medicines Agency (EMEA) [8] recommend that hepatic impairment is defined in clinical studies by the Child-Pugh score, which is generally used to assess the status of chronic liver diseases, mainly cirrhosis. There is some concern, however, that studies conducted in patients with cirrhosis may not be clinically relevant or predictive of effects in patients with liver metastases [9, 10]. Alternative methods of classifying liver impairment have been devised in an attempt to provide a more clinically meaningful definition of hepatic dysfunction in this population, including a scoring system based on conventional liver biochemistry tests [10].

Gefitinib (IRESSA^{TM}, AstraZeneca, London, UK) is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor with antitumor activity in patients with advanced non-small-cell lung cancer [NSCLC] [11–14]. Gefitinib undergoes extensive hepatic metabolism, predominantly by cytochrome P450 CYP3A4 and also by CYP2D6, and is excreted in bile as parent compound and metabolites, mostly O-desmethyl gefitinib, which is inactive [15–17]. This paper describes two studies investigating the pharmacokinetics and tolerability of gefitinib in patients with hepatic impairment due to cirrhosis (Study 1, D7913C00718) or hepatic metastases (Study 2, 1839IL/0032).

Methods

Study subjects

Both studies were conducted in compliance with Good Clinical Practice according to the Declaration of Helsinki. Each study center obtained Ethics Committee approval, and all volunteers and patients provided written informed consent.

Study 1 recruited patients aged 18–75 years with confirmed liver disease classified by Child-Pugh criteria [18] and a control group of healthy volunteers selected to match the moderate hepatic impairment group for sex, age, and weight. Exclusion criteria included current or recent treatment with a CYP3A4 inducer or inhibitor, a CYP2D6 inhibitor, or treatment with a hepatotoxic drug within the past 3 months and fluctuating or rapidly deteriorating hepatic function. Treatment with a gastric pH modulator was only allowed in the severe hepatic impairment group and was discontinued 24 h prior to dosing with gefitinib.

Study 2 recruited patients aged ≥18 years with a solid malignant tumor refractory to standard therapy or for which no standard therapy was available, a World Health Organization performance status of 0–2 and a life expectancy of ≥8 weeks. They had normal or impaired liver function, according to liver biochemistry tests. Exclusion criteria included current or recent treatment with a CYP3A4 inhibitor and newly diagnosed intracerebral metastases.

Study design

Both studies had an open, parallel-group, multicenter design. Study 1 was conducted at five centers in the Czech Republic between November 2004 and October 2005. Study 2 was conducted at four centers in the UK between November 2000 and December 2001.

In Study 1, patients with liver disease were assigned to one of three groups (mild, moderate, and severe hepatic impairment) according to the Child-Pugh classification [18]. All patients and healthy volunteers were given a single oral dose of gefitinib 250 mg on day 1 following an overnight fast. Concomitant medication was not allowed unless the investigator had given approval.

In Study 2, patients were assigned to one of three groups (normal, moderate, and severe hepatic impairment) based on alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels [10]. Each parameter was given a CTC grade of 0–4, and the three values summed to give a total score ranging from 0 to 12. Hepatic function was defined as 'normal' (scores of 0–2), 'moderately impaired' (3–5), or 'severely impaired' (6–12). Patients with moderate or severe hepatic impairment were required to have radiologically proven liver metastases. Patients received two 250 mg doses of gefitinib taken 12 h apart on day 1, followed by 250 mg once daily on days 2–28. Concomitant systemic anticancer treatment or radiotherapy was not permitted, apart from palliative radiotherapy in patients with isolated symptomatic bone metastases.

For both studies, screening assessments included physical examination, medical history, hematology and clinical chemistry, vital signs, 12-lead electrocardiogram, and clinical evaluation. Tolerability was evaluated during both studies by monitoring of adverse events, clinical chemistry, hematology, urinalysis, vital signs, and ophthalmologic assessments (Study 2 only).

Pharmacokinetic assessment

In Study 1, blood samples were collected before the dose, at 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h after the dose, and then at 24-h intervals up to 10 days after dosing. For Study

2, blood samples were collected before the dose on days 2, 8, 15, and 22, and before the dose, and then at 1, 3, 5, 7, 10 and 24 h after the dose on day 28. Plasma samples were stored at −20°C pending analysis.

Each plasma sample was analyzed for gefitinib and its metabolite, O-desmethyl gefitinib. Gefitinib was quantified using high-performance liquid chromatography with tandem mass spectrometric detection (HPLC–MS/MS) by Eurofins Medinet BV, The Netherlands [19]. O-desmethyl gefitinib was quantified using reversed phase HPLC by Eurofins Medinet BV, The Netherlands (Study 1) or the Drug Metabolism and Pharmacokinetics Department, AstraZeneca UK (Study 2) (*data on file*).

Pharmacokinetic analysis

In both studies, pharmacokinetic parameters for gefitinib and O-desmethyl gefitinib were determined from the plasma concentration data using non-compartmental methods (WinNonlin Professional Version 3.1, Pharsight Corporation, USA). All pharmacokinetic parameters were calculated after a single dose in Study 1 and at steady state in Study 2 (day 28). Attainment of steady state was estimated by visual comparison of minimum plasma concentrations (C_{min}) of gefitinib throughout the dosing period.

The predefined primary pharmacokinetic endpoint was the gefitinib $AUC_{0-\infty}$ for Study 1 and the AUC_{24}^{SS} for Study 2.

Secondary endpoints were as follows:

Study 1 Gefitinib maximum plasma concentration (C_{max}), t_{max}, $t_{½}$, and CL/F; O-desmethyl gefitinib $AUC_{0-\infty}$, $C_{max,}$ t_{max}, and $t_{1/2}$.

Study 2 Gefitinib C_{max}^{SS}, C_{min}^{SS}, t_{max}, CL/F; O-desmethyl gefitinib AUC_{24}^{SS}, C_{max}^{SS}, C_{min}^{SS}, $t_{max.}$

C_{max}, C_{min}, and t_{max} were determined by inspection of the plasma concentration–time profiles. The rate constant of the slowest disposition phase (λz) was calculated by log-linear regression of the terminal portion of the concentration–time profiles where there were sufficient data and $t_{½}$ was calculated as $0.693/\lambda z$. AUC up to the time of the last quantifiable plasma concentration (AUC_{0-t}) and AUC_{24}^{SS} were calculated using the linear trapezoid rule. AUC_{0-t} was extrapolated to infinity using λz to obtain $AUC_{0-\infty}$. CL/F was calculated as the dose received divided by the $AUC_{0-\infty}$ or AUC_{24}^{SS}.

Statistical analysis

Patients were considered evaluable if they received a single dose of gefitinib in Study 1 or completed the 28-day study period in Study 2 and if plasma sampling was adequate to allow determination of gefitinib $AUC_{0-\infty}$ or AUC_{24}^{SS}. The potential impact of all concomitant medications taken during the study on the pharmacokinetics of gefitinib was assessed before inclusion of the pharmacokinetic data in the statistical analysis. Gefitinib $AUC_{0-\infty}$ or AUC_{24}^{SS} values for each of the hepatic impairment groups were compared with the corresponding normal hepatic function group. The exception was the severe hepatic impairment group in Study 2, where the numbers were too small to allow statistical analysis. After logarithmic transformation, an analysis of variance model was fitted allowing for the effects of hepatic impairment. Results are presented in terms of adjusted gmeans, the ratio of the gmeans (hepatic impairment:normal function), and the upper bound of the one-sided 95% CI for this ratio. Hepatic impairment would be considered to significantly increase exposure to gefitinib if the CI upper limit lay above 2.0. This magnitude of change was considered acceptable because a doubling in exposure following a 250 mg dose would be equivalent to administration of a 500 mg dose, where clinical experience has shown good tolerability [12, 13].

Power calculations indicated that 10 (Study 1) or 12 (Study 2) evaluable subjects per group would be required to ensure at least an 80% chance of detecting a statistically significant effect.

Results

Hepatic impairment due to cirrhosis (Study 1)

Demography and baseline characteristics

Study 1 recruited 10 healthy volunteers and 30 patients with cirrhosis (10 each with Child-Pugh mild, moderate and severe hepatic impairment). All subjects received a single dose of gefitinib 250 mg and were included in the pharmacokinetic and tolerability analyses. Demographic parameters, Child-Pugh scores, and hepatic impairment scores calculated according to the criteria used in Study 2 are summarized in Table 1.

Pharmacokinetics

Gefitinib Geometric mean (Gmean) plasma concentration–time profiles of gefitinib following a single 250 mg dose are shown in Fig. 1. Plasma concentrations of gefitinib declined biphasically beyond the peak with the last measurable concentration present at around 120 h after dosing. In patients with hepatic impairment, however, gefitinib was still quantifiable at 168 h (mild) or 240 h (moderate and severe).

Pharmacokinetic parameters for gefitinib are summarized in Table 2. Gmean area under the gefitinib plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) was significantly higher for patients with all grades of

Table 1 Demographic parameters and liver function test results at baseline for healthy volunteers and patients with hepatic impairment due to cirrhosis (Study 1) and for patients with normal hepatic function or hepatic impairment due to liver metastases (Study 2)

Study 1	Healthy volunteers ($n = 10$)	Mild hepatic impairment ($n = 10$)	Moderate hepatic impairment ($n = 10$)	Severe hepatic impairment ($n = 10$)
Demographic parameters				
Age, years (mean ± SD [range])	53.3 ± 7.9 [33–60]	51.3 ± 11.0 [27–61]	52.9 ± 9.3 [33–63]	57.4 ± 3.4 [53–63]
Weight, kg (mean ± SD [range])	74.6 ± 9.8 [63–94]	77.5 ± 18.5 [53–109]	74.0 ± 12.1 [59–100]	77.1 ± 12.1 [64–99]
Sex (male/female), *n*	7/3	5/5	7/3	6/4
Race (Caucasian), *n*	10	10	10	10
Liver function tests				
AST (U/L) (mean ± SD)	21.2 ± 3.4	33.9 ± 25.6	61.3 ± 30.0	45.5 ± 16.4
ALP (U/L) (mean ± SD)	79.2 ± 22.4	89.4 ± 31.2	173.7 ± 76.3	102.7 ± 37.1
Bilirubin (μmol/l) (mean ± SD)	11.0 ± 4.7	15.4 ± 5.1	33.6 ± 15.9	52.4 ± 31.4
Child-Pugh score (n)				
Mild impairment (5–6)	N/A	10	0	0
Moderate impairment (7–9)		0	10	0
Severe impairment (10–15)		0	0	10
Mean ± SD (range)		5.1 ± 0.3 (5–6)	7.2 ± 0.4 (7–8)	11.2 ± 1.6 (10–14)
Hepatic function score (n)[a]				
Normal (0–2)	N/A	10	5	5
Moderate impairment (3–5)		0	5	5
Severe impairment (6–12)		0	0	0
Mean ± SD (range)	N/A	0.5 ± 0.7 (0–2)	2.6 ± 1.5 (0–4)	2.5 ± 1.2 (0–4)

Study 2	Normal hepatic function ($n = 18$)	Moderate hepatic impairment ($n = 16$)	Severe hepatic impairment ($n = 7$)
Demographic parameters			
Age, years (mean ± SD [range])	58.1 ± 12.0 [32–77]	59.2 ± 9.1 [34–71]	57.7 ± 10.9 [46–72]
Weight, kg (mean ± SD [range])	68.4 ± 15.9 [44.2–119.0]	69.6 ± 14.1 [47.0–95.7]	61.8 ± 8.2 [53.7–76.3]
Sex (male/female), *n*	6/12	7/9	2/5
Race (Caucasian/Asian), *n*	17/1	16/0	7/0
Liver function tests			
AST (U/L) (mean ± SD)	33.3 ± 36.9	85.2 ± 31.7	123.0 ± 47.9
ALP (U/L) (mean ± SD)	189.8 ± 99.1	1,066.6 ± 974.4	1,986.7 ± 791.9
Bilirubin (μmol/l) (mean ± SD)	8.1 ± 2.4	16.9 ± 9.4	94.7 ± 103.1
Hepatic function score (n)[a]			
Normal (0–2)	18	0	0
Moderate impairment (3–5)	0	16	0
Severe impairment (6–12)	0	0	7

AST Aspartate aminotransferase, *ALP* Alkaline phosphatase, *SD* Standard deviation

[a] Based on liver biochemistry tests

hepatic impairment compared with healthy volunteers. Estimated gmean $AUC_{0-\infty}$ ratios (impaired:normal) for the mild, moderate, and severe hepatic impairment groups were 1.40, 3.63, and 2.66, respectively, with upper bounds of the one-sided 95% CI of 2.51, 6.51, and 4.78.

Gefitinib was absorbed moderately slowly, and there was no apparent change in time to maximum plasma concentration (t_{max}) with increased severity of hepatic impairment. Peak plasma levels of gefitinib were generally higher in patients with hepatic impairment.

Terminal half-life ($t_{1/2}$) was approximately doubled in patients with moderate or severe hepatic impairment compared with healthy volunteers. Oral plasma clearance (CL/F) of gefitinib was lower by approximately 30, 70, and

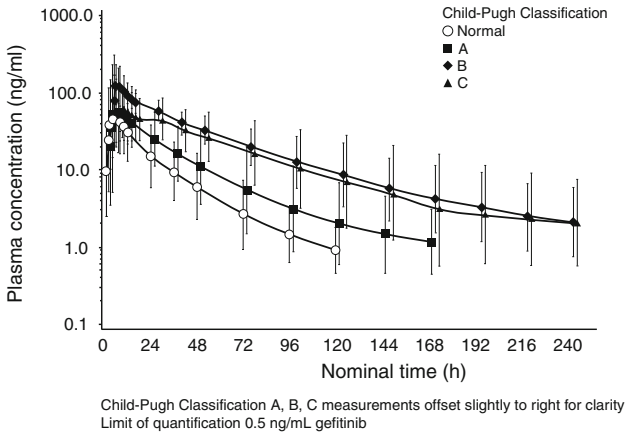

Fig. 1 Gmean (±SD) plasma concentration–time profiles of gefitinib in healthy volunteers and patients with hepatic impairment due to cirrhosis ($n = 10$ per group) after a single oral dose of 250 mg gefitinib (Study 1). *Child-Pugh hepatic impairment classification* **a** mild, **b** moderate, and **c** severe

60% in the groups with mild, moderate, and severe hepatic impairment, respectively.

O-desmethyl gefitinib Pharmacokinetic parameters for O-desmethyl gefitinib are summarized in Table 2. As the severity of hepatic impairment increased, the rate of metabolism to O-desmethyl gefitinib decreased as indicated by the observed increase in t_{max} and lower peak concentrations were seen. $t_{1/2}$ of O-desmethyl gefitinib was approximately doubled in the group with moderate hepatic impairment compared with healthy volunteers and patients with mild hepatic impairment. Very low concentrations of O-desmethyl gefitinib were detected in patients with severe hepatic impairment, and the plasma concentration data were only sufficient to calculate $AUC_{0-\infty}$ and $t_{1/2}$ in one patient in this group. The metabolite:gefitinib $AUC_{0-\infty}$ ratio appeared to be lower in patients with moderate hepatic impairment compared with healthy volunteers and those with mild hepatic impairment (Fig. 2).

Tolerability

None of the healthy volunteers reported adverse events. A total of 13 adverse events occurred in eight patients with hepatic impairment due to cirrhosis (4, 2, and 2 in the mild, moderate, and severe groups, respectively). All adverse events were consistent with those expected in patients with cirrhosis, and none were considered related to gefitinib. Only one serious adverse event was reported; this was National Cancer Center Institute Common Toxicity Criteria (CTC) Grade 3 hematemesis in a patient with moderate hepatic impairment. There were no clinically relevant changes in hematology, clinical chemistry, urinalysis, or physical examination in any of the groups.

Table 2 Summarized pharmacokinetic parameters of gefitinib and its metabolite, O-desmethyl gefitinib, after a single oral dose of 250 mg of gefitinib in healthy volunteers and patients with hepatic impairment due to cirrhosis (Study 1)

	Healthy volunteers ($n = 10$)	Mild hepatic impairment ($n = 10$)	Moderate hepatic impairment ($n = 10$)	Severe hepatic impairment ($n = 10$)
Gefitinib				
$AUC_{0-\infty}$ (ng h/ml) [gmean (CV%)]	1,415 (80.7) [$n = 9$]	1,980 (115.7)	5,137 (44.5)	3,768 (103.9)
C_{max} (ng/ml) [gmean (CV%)]	57.5 (99.5)	82.8 (109.7)	155.7 (52.9)	69.6 (78.8)
t_{max} (h) [median (range)]	4 (2–8)	5 (2–6)	2 (1–10)	3 (1–48)
$t_{½}$ (h) (mean ± SD)	23.8 ± 8.9 [$n = 9$]	32.1 ± 15.1	47.9 ± 16.2	47.4 ± 19.8
CL/F (ml/min) [gmean (CV%)]	2,944 (80.7) [$n = 9$]	2,105 (115.7)	811 (44.5)	1,106 (103.9)
O-desmethyl gefitinib				
$AUC_{0-\infty}$ (ng h/ml) [gmean (CV%)]	1,448 (99.8) [$n = 9$]	2,958 (63.4) [$n = 6$]	1,752 (103.1) [$n = 8$]	NC
C_{max} (ng/ml) [gmean (CV%)]	76.2 (143.8)	44.7 (345.9)	44.1 (77.6)	10.4 (204.9)
t_{max} (h) [median (range)]	2 (1–10)	8 (2–24)	8 (6–12)	24 (6–36)
$t_{1/2}$ (h) (mean ± SD)	21.2 ± 6.0 [$n = 9$]	23.4 ± 8.2 [$n = 6$]	41.7 ± 24.6 [$n = 8$]	NC

$AUC_{0-\infty}$ Area under the plasma concentration–time curve from zero to infinity, *gmean* Adjusted geometric mean, *CV* Coefficient of variation, *C_{max}* Maximum plasma concentration, *t_{max}* Time of maximum plasma concentration, *$t_{½}$* Terminal half-life, *CL/F* Oral clearance, *NC* Not calculated, *SD* Standard deviation

Patient numbers vary since pharmacokinetic variables were only calculated where sufficient data points were available

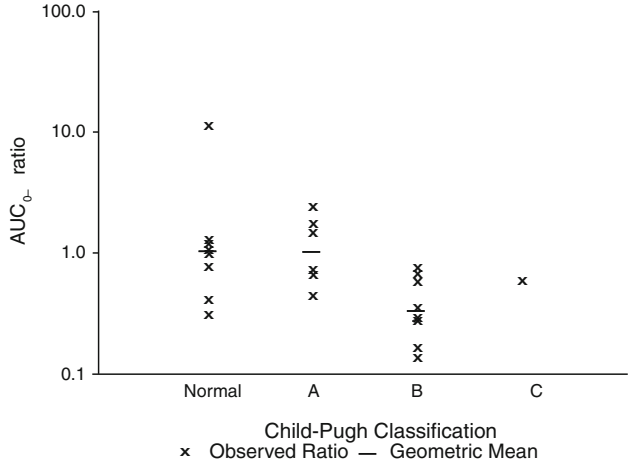

Fig. 2 O-*desmethyl gefitinib* $AUC_{0-\infty}$ ratios in healthy volunteers and patients with hepatic impairment due to cirrhosis ($n = 10$ per group) after a single oral dose of 250 mg gefitinib (Study 1). $AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity. *Child-Pugh hepatic impairment classification* **a** mild, **b** moderate, and **c** severe

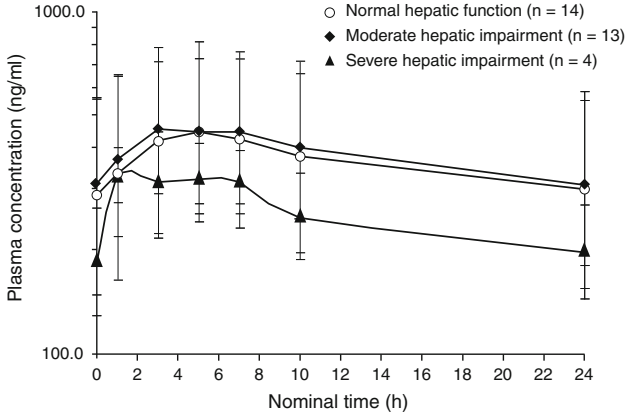

Fig. 3 Gmean (±SD) plasma concentration–time profiles of gefitinib on day 28 following multiple oral doses of 250 mg gefitinib once daily in patients with normal hepatic function ($n = 18$) or moderate ($n = 16$) or severe ($n = 7$) hepatic impairment due to liver metastases (Study 2)

Hepatic impairment due to liver metastases (Study 2)

Demography and baseline characteristics

Forty-one patients were included in Study 2, of whom 18 had normal hepatic function, 16 had moderate hepatic impairment, and seven had severe hepatic impairment according to pre-defined biochemical criteria and liver metastases. Six patients (two from each group) did not complete 28 days of study medication, and a further four patients (two normal, one moderately impaired, one severely impaired) had insufficient blood sampling on day 28 to determine the primary endpoint, area under the curve during the 24-h dosing interval at steady state (AUC_{24}^{ss}). The pharmacokinetic evaluation included 27 patients (14 normal, 13 moderately impaired). Pharmacokinetic data from the four patients with severe hepatic dysfunction were summarized but not included in the statistical analysis due to the small sample size. All 41 patients were evaluable for tolerability.

Five patients missed a dose of gefitinib during the 28-day pharmacokinetic treatment period. Two of these patients (normal hepatic function) were included in the statistical analysis since these dose interruptions were not considered to affect their steady-state pharmacokinetics. The remaining three patients who missed doses (severe hepatic impairment) were not, in any case, included in the statistical analysis.

Demographic parameters and liver biochemistry test results for the three groups at baseline are summarized in Table 1. The groups were similar with respect to all the demographic characteristics, apart from gender. All patients recruited had solid malignant tumors, predominantly breast, colorectal, and non-small-cell lung carcinomas. All patients with hepatic impairment had radiologically confirmed liver metastases.

Pharmacokinetics

Gefitinib Gmean plasma concentration–time profiles of gefitinib following the 250 mg dose on day 28 are shown in Fig. 3 and steady-state pharmacokinetic parameters for gefitinib are summarized in Table 3. Gmean gefitinib AUC_{24}^{SS} was slightly higher for patients with moderate liver impairment compared with those with normal hepatic function, although the difference was not statistically significant (estimated gmean AUC_{24}^{SS} ratio: 1.07, upper limit of the one-sided 95% CI 1.55). Plasma concentrations of gefitinib tended to be lower in the four patients with severe hepatic impairment than in normal patients, with a gmean AUC_{24}^{SS} value of 6,226 ng h/ml.

Gefitinib steady state was achieved by the time of the first assessment (day 8) in all patients, irrespective of hepatic function (*data not shown*). There were no marked differences in the pharmacokinetic profile of gefitinib between patients with normal liver function and moderate hepatic impairment (Table 3). Although there were only four patients with severe hepatic impairment, the pharmacokinetic parameters for gefitinib in this group were broadly similar to those seen in patients with normal liver function. At steady state, peak concentrations of gefitinib were reached relatively slowly in all groups, with t_{max} typically ranging from 3 to 7 h. Similar steady-state peak and trough plasma concentrations of gefitinib were also observed in the three patient groups. Oral plasma clearance

Table 3 Summarized steady-state pharmacokinetic parameters of gefitinib and its metabolite, O-desmethyl gefitinib, after multiple oral doses of 250 mg gefitinib once daily in patients with normal hepatic function or hepatic impairment due to liver metastases (Study 2)

	Normal hepatic function	Moderate hepatic impairment	Severe hepatic impairment
Gefitinib	($n = 14$)	($n = 13$)	($n = 4$)
AUC_{24}^{SS}, ng h/ml (gmean (CV%) [range])	8,896 (55) [3,300–26,200]	9,553 (66) [2,320–23,300]	6,226 (24) [4,850–8,550]
C_{max}^{SS}, ng/ml (gmean (CV%) [range])	466.4 (52.6) 176–1,230]	517.7 (66.5) [138–1,120]	371.8 (23.5) [264–428]
t_{max}, h [median (range)]	5 (3–7)	3 (1–9)	2 (1–7)
C_{min}^{SS}, ng/ml [gmean (CV%)]	291.2 (66.5)	313.1 (68.0)	184.7 (37.3)
CL/F, ml/min [gmean (CV%)]	472 (55)	445 (64)	669 (24)
O-desmethyl gefitinib	($n = 17$)	($n = 15$)	($n = 5$)
AUC_{24}^{SS}, ng h/ml [g mean (CV%)]	7,370 (101) [$n = 12$]	4,170 (102) [$n = 11$]	3,470 (115) [$n = 4$]
AUC_{24}^{SS} as % of gefitinib AUC_{24}^{SS} [gmean (CV%)]	87.3 (103) [$n = 12$]	52.3 (127) [$n = 11$]	57.3 (118) [$n = 4$]
C_{max}^{SS}, ng/ml (range)	14.8–1,520 ($n = 13$)	31.3–764 ($n = 11$)	47.7–434 ($n = 4$)
t_{max}, h (range)	0–24 ($n = 13$)	1–24 ($n = 11$)	1–24 ($n = 4$)
C_{min}^{SS}, ng/ml (range)			
Day 2	<5–436	<5–243	27.6–67.2
Day 8	<5–663	<5–553 ($n = 14$)	26.0–519
Day 15	<5–551 ($n = 16$)	<5–691	16.2–389
Day 22	<5–790 ($n = 14$)	<5–624 ($n = 13$)	19.6–315
Day 28	<5–999 ($n = 14$)	<5–407 ($n = 14$)	35.0–346 ($n = 4$)

AUC_{24}^{SS} Area under the plasma concentration–time curve during the 24-h dosing interval at steady state, *CV* Coefficient of variation, *C_{max}^{SS}* Maximum steady-state plasma concentration during the dosing interval, *t_{max}* Time of maximum plasma concentration, *C_{min}^{SS}* Minimum steady-state plasma concentration during the dosing interval, *CL/F* Oral clearance

Patient numbers vary since pharmacokinetic variables were only calculated where sufficient data points were available

of gefitinib did not appear to be influenced by hepatic impairment due to liver metastasis.

O-desmethyl gefitinib Pharmacokinetic parameters for O-desmethyl gefitinib are summarized in Table 3. The AUC_{24}^{SS} for O-desmethyl gefitinib following 28 days of dosing showed high inter-individual variability in all three groups of patients, with coefficients of variation of 101, 102, and 115% in patients with normal hepatic function, moderate impairment, and severe impairment, respectively. When expressed relative to exposure to parent drug, O-desmethyl gefitinib AUC_{24}^{SS} represented 87, 52, and 57% (mean values) of the gefitinib AUC_{24}^{SS} exposure in the normal, moderate, and severely impaired patients, respectively. Comparison of the concentrations present before the dose and 24 h after the dose on day 28 confirmed steady-state exposure to O-desmethyl gefitinib.

With such wide variability in the exposure values across all three groups, there was no discernable difference in exposure to O-desmethyl gefitinib due to differing degrees of hepatic function impairment.

Tolerability

No clear differences were seen in the adverse-event profile between the three patient groups. All 41 patients reported at least one adverse event, although many of these were consistent with the underlying disease. Adverse events considered related to trial medication occurred in 17 patients (94%) with normal hepatic function, 15 (94%) with moderate hepatic impairment, and six (86%) with severe hepatic impairment. The most common treatment-related adverse events were diarrhea (8 [44], 9 [56], and 5 [71%] patients with normal hepatic function, moderate, and severe hepatic impairment, respectively) and rash (10 [56], 7 [44], and 3 [43%] patients, respectively) (Table 4).

Two patients had CTC Grade 4 adverse events that were considered related to trial medication; one had a peptic ulcer that was also attributed to carcinomatosis, and the other had a pulmonary embolus. The first patient died following a subsequent gastrointestinal hemorrhage, which was not considered to be treatment related. The second had a pulmonary embolus, which was treated with anticoagulants, but did not lead to withdrawal from study medication. CTC Grade 3 treatment-related adverse events were reported by a further three patients with normal hepatic function (diarrhea and hyponatremia; vomiting; increased ALT; and AST), four patients with moderate hepatic impairment (diarrhea; vomiting; acne; dry skin), and one patient with severe hepatic impairment (rash). Three patients were withdrawn from treatment due to treatment-related adverse events: one with normal hepatic function

Table 4 Treatment-related adverse events that were reported by more than one patient overall in patients with normal hepatic function or hepatic impairment due to liver metastases (Study 2)

	Number of patients		
	Normal hepatic function ($n = 18$)	Moderate hepatic impairment ($n = 16$)	Severe hepatic impairment ($n = 7$)
Diarrhea	8	9	5
Rash	10	7	3
Dry skin	4	7	0
Nausea	4	6	1
Vomiting	4	3	0
Eye pain	3	1	2
Conjunctivitis	3	2	0
Stomatitis	3	2	0
Asthenia	1	4	0
Taste perversion	1	3	1
Anorexia	3	1	0
Pruritus	3	1	0
Somnolence	3	1	0
Dry eyes	2	1	1
Acne	0	3	1
Dry mouth	0	3	0
Eczema	1	1	0
ALT increased	1	1	0
AST increased	1	1	0

ALT Alanine aminotransferase, *AST* Aspartate aminotransferase

(increased ALT and AST) and two with moderate hepatic impairment (peptic ulcer and gastrointestinal hemorrhage; dry skin).

As expected, the three patient groups differed at baseline with respect to AST, alkaline phosphatase, and bilirubin (Table 1), and these differences were maintained throughout the study. There were no other clinically significant differences between the groups in clinical chemistry, hematology, urinalysis, vital signs, or ophthalmologic assessments.

Discussion

Liver metastases are the most common cause of hepatic dysfunction in patients with advanced cancer. Assessment of the pharmacokinetic profile of new oncology drugs in patients with liver metastases is thus clinically relevant since exposure to the drug may be increased in this population. Although there is no universally accepted grading scheme for hepatic impairment in clinical studies, FDA and EMEA guidelines endorse the use of the Child-Pugh classification [7, 8, 18]. We investigated the pharmacokinetics of gefitinib in subjects with hepatic impairment due to cirrhosis (Study 1) and liver metastases (Study 2).

Study 1 showed that the pharmacokinetic characteristics of gefitinib following a single 250 mg dose were significantly altered in patients with hepatic impairment due to cirrhosis compared with healthy volunteers. Although pharmacokinetic changes were generally greater in patients with moderate or severe hepatic impairment, a clinically relevant effect was also seen in patients with mild hepatic impairment. The presence of cirrhosis resulted in a longer half-life and reduced plasma clearance, leading to at least a doubling of exposure to gefitinib. These effects could be the result of reduced systemic metabolic clearance or a reduction in first-pass metabolism with a consequent increase in bioavailability. The changes in systemic handling of gefitinib seen in these patients are consistent with a drug that is primarily cleared by the liver.

It should be noted that inter-patient variability in the $AUC_{0-\infty}$ for healthy volunteers in this study was greater than that observed in previous studies [20, 21]. This observation suggests that estimates of mean values may not be accurate since variability was high and the groups were small. Since it is known that protein binding can be altered in patients with hepatic impairment, it is recommended that consideration be given to the free fraction for drugs that are highly extracted from the liver and extensively protein bound [7]. However, gefitinib is approximately 91% bound to plasma proteins in human plasma [15] and is considered to be a medium:high extraction ratio compound, and hence, alterations in protein binding due to hepatic impairment are unlikely to influence hepatic metabolism to a meaningful extent [22].

In contrast to the effects seen in patients with cirrhosis, Study 2 provided no clear evidence of a clinically relevant increase in exposure to gefitinib when given to patients with moderate hepatic impairment due to liver metastases. Although gefitinib AUC_{24}^{SS} was slightly higher in patients with moderate hepatic dysfunction compared with those with normal liver function, this difference was neither statistically nor clinically significant. Steady state was reached by the 8th day of treatment with gefitinib in all patients, irrespective of hepatic status. Peak steady-state plasma concentrations and plasma clearance of gefitinib appeared to be unaffected by the presence of liver metastases. There was no evidence of higher exposure to gefitinib in a small number of patients with severe hepatic impairment. Furthermore, the pharmacokinetic parameters of gefitinib and the level of variability in gefitinib plasma levels determined in the present study are broadly consistent with previously published pharmacokinetic data in cancer patients [21, 23–26]. Although plasma levels of O-desmethyl gefitinib were also very variable, there were

no obvious changes due to impaired hepatic function. This lack of influence on the metabolic clearance of gefitinib is consistent with a lack of effect on the pharmacokinetics of the parent compound.

The classification of hepatic dysfunction in the context of anticancer drug development is complex, and the Child-Pugh criteria have important limitations. On the one hand, patients with neither clinical nor biochemical evidence of liver failure are classified as having 'mild' hepatic impairment. By contrast, anticancer drug therapy would rarely be appropriate in a patient with severe Child-Pugh liver impairment as such patients with extensive liver metastases would usually be close to the end of their lives. Indeed, it is those patients with no overt clinical signs of liver failure, but whose liver biochemistry tests are deranged, who pose the main clinical challenge.

More sophisticated direct measures of liver function have not proved useful in this setting, so the use of liver biochemistry tests is attractive [9]. The National Cancer Institute Organ Dysfunction Working Group has derived a set of criteria based on serum bilirubin and AST levels [9, 27]. This classification distributed patients more evenly across four categories than the Child-Pugh system. Specifically, more than half of those in the 'mild' Child-Pugh impairment group were in the mild or moderate impairment groups using the biochemical classification. In our study in patients with cirrhosis, all those with mild hepatic impairment and half in each of the moderate and severe hepatic impairment groups according to Child-Pugh score were considered to have normal hepatic function when classified according to liver enzyme levels alone. Clearly, the findings from patients with liver metastases in Study 2 are more clinically relevant since the current target population for gefitinib is advanced cancer.

In the broader context of anticancer drug development, pharmacokinetic studies of other hepatically cleared drugs have shown varying results. Studies of 5-fluorouracil and antipyrine in patients with liver metastases have suggested that the liver has a large functional reserve, even in the presence of massive tumor infiltration [28, 29]. By contrast, raised liver biochemistry tests are associated with reduced clearance of the anthracyclines doxorubicin [30] and epirubicin [31]. A recent study in cancer patients reported higher plasma concentrations of tipifarnib, a drug that undergoes extensive hepatic metabolism, in patients with Child-Pugh mild or moderate liver impairment [32]. It would seem most appropriate to evaluate anticancer drugs in patients with liver metastases and hepatic impairment using a biochemical classification scheme in parallel with an indication of their status using Child-Pugh classification. The increasing incidence of hepatitis C carriage in the global population [33] will, however, increase the possibility of patients with cirrhosis developing cancer, so the findings from Study 1 provide an useful indication of the type of pharmacokinetic effects that might be expected in patients with cancer and comorbid liver cirrhosis.

All adverse events reported in Study 1 were consistent with those expected in patients with cirrhosis. The safety profile of gefitinib observed in Study 2 in patients with hepatic impairment due to liver metastases was comparable to that seen in patients with normal hepatic function in this and previous studies [23–26]. There was no evidence of any clinically relevant safety concerns in either study. In Study 2, patients from the moderate and severe hepatic impairment groups remained on gefitinib treatment for up to 10 months with no evidence of deterioration in the safety profile.

In conclusion, we have shown that different pharmacokinetic outcomes may result from testing patient populations with hepatic impairment of different underlying etiology and classification. Consequently, careful thought must be given to the clinical interpretation of these results. The conventional Child-Pugh study detected differences in the systemic handling of gefitinib in patients with hepatic impairment due to cirrhosis. In contrast, the experimental approach provided no evidence that moderate hepatic impairment due to liver metastases affected the pharmacokinetics or tolerability of gefitinib suggesting that no dose adjustment is warranted in this population. Gefitinib should be used with caution in patients with advanced cancer and severe hepatic impairment due to liver metastases and in those with cirrhosis of the liver.

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Conflict of interest Chris Twelves has acted as a consultant to AstraZeneca and as a member of a data safety monitoring board for Roche. Mark Verrill has acted as a consultant and received honoraria and research support from Roche. James Carmichael, Alison Holt, Mireille Cantarini, Merran Macpherson, and Helen Swaisland are employees and shareholders of AstraZeneca. Alan Swaisland was an employee of AstraZeneca at the time when these studies were conducted and is a shareholder.

References

1. Donelli MG, Zucchetti M, Munzone E, D'Incalci M, Crosignani A (1998) Pharmacokinetics of anticancer agents in patients with impaired liver function. Eur J Cancer 34:33–46

2. Sotaniemi EA, Niemelä O, Risteli L, Stenbäck F, Pelkonen RO, Lahtela JT, Risteli J (1986) Fibrotic process and drug metabolism in alcoholic liver disease. Clin Pharmacol Ther 40:46–55
3. Robieux I, Sorio R, Borsatti E, Cannizzaro R, Vitali V, Aita P, Freschi A, Galligioni E, Monfardini S (1996) Pharmacokinetics of vinorelbine in patients with liver metastases. Clin Pharmacol Ther 59:32–40
4. Kolesar JM (2000) Docetaxel in hepatic impairment. J Oncol Pharm Prac 6:43–49
5. Clarke SJ, Rivory LP (1999) Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 36:99–114
6. Chao Y, Chan WK, Birkhofer MJ, Hu OY, Wang SS, Huang YS, Liu M, Whang-Peng J, Chi KH, Lui WY, Lee SD (1998) Phase II and pharmacokinetic study of paclitaxel therapy for unresectable hepatocellular carcinoma patients. Br J Cancer 78:34–39
7. US Department of Health and Human Services Food and Drug Administration (2003) Guidance for industry. Pharmacokinetics in patients with impaired hepatic function: study design, data analysis and impact on dosing and labeling. US food and drug administration. http://www.fda.gov/cber/gdlns/imphep.pdf. Accessed 9 Jan 2009
8. European Medicines Agency. Committee for medicinal products for human use (2005) Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. European medicines agency. http://www.emea.europa.eu/pdfs/human/ewp/233902en.pdf. Accessed 8 Jan 2009
9. Twelves CJ (2006) Special populations and interaction studies. In: Eisenhauser EA, Twelves C, Buyse M (eds) Phase I cancer clinical trials: a practical guide. Oxford University Press, Oxford, pp 95–137
10. Twelves C, Glynne-Jones R, Cassidy J, Schüller J, Goggin T, Roos B, Banken L, Utoh M, Weidekamm E, Reigner B (1999) Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. Clin Cancer Res 5:1696–1702
11. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K (2005) Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa survival evaluation in lung cancer). Lancet 366:1527–1537
12. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard J-Y, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong R-P, Baselga J (2003) Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 21:2237–2246
13. Kris MG, Natale RB, Herbst RS, Lynch TJ Jr (2003) Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 290:2149–2158
14. Mok TS, Wu Y-L, Thomgprasert S, Yang C-H, Chu D-T, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang J-J, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947–957
15. McKillop D, Hutchison M, Partridge EA, Bushby N, Cooper CM, Clarkson-Jones JA (2004) Metabolic disposition of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor: in rat, dog and man. Xenobiotica 34:917–934
16. McKillop D, McCormick AD, Millar A, Miles GS, Phillips PJ, Hutchison M (2005) Cytochrome P450-dependent metabolism of gefitinib. Xenobiotica 35:39–50
17. Laight A, Swaisland H, Partridge EA, Yates RA, Dickson JEA, Grisedale HM, McCracken NW, Heron WJ, Hutchison M (2002) Metabolism of [^{14}C]-ZD1839 ('Iressa') in healthy male volunteers. Poster presented at ESMO, Nice
18. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973) Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60:646–649
19. Jones HK, Stafford LE, Swaisland HC, Payne R (2002) A sensitive assay for ZD1839 (Iressa) in human plasma by liquid-liquid extraction and high performance liquid chromatography with mass spectrometric detection: validation and use in Phase I clinical trials. J Pharm Biomed Anal 29:221–228
20. Swaisland H, Laight A, Stafford L, Jones H, Morris C, Dane A, Yates R (2001) Pharmacokinetics and tolerability of the orally active selective epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in healthy volunteers. Clin Pharmacokinet 40:297–306
21. Swaisland HC, Smith RP, Laight A, Kerr DJ, Ranson M, Wilder-Smith CH, Duvauchelle T (2005) Single-dose clinical pharmacokinetic studies of gefitinib. Clin Pharmacokinet 44:1165–1177
22. Rowland M, Tozer TN (1995) Clinical pharmacokinetics: concepts and applications, 3rd edn. Lippincott Williams and Wilkins, Baltimore
23. Nakagawa K, Tamura T, Negoro S, Kudoh S, Yamamoto N, Yamamoto N, Takeda K, Swaisland H, Nakatani I, Hirose M, Dong R-P, Fukuoka M (2003) Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol 14:922–930
24. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, Kaye SB, Gianni L, Harris A, Bjork T, Averbuch SD, Feyereislova A, Swaisland H, Rojo F, Albanell J (2002) Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839: a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 20:4292–4302
25. Herbst RS, Maddox A-M, Rothenberg ML, Small EJ, Rubin EH, Baselga J, Rojo F, Hong WK, Swaisland H, Averbuch SD, Ochs J, Mucci LoRusso P (2002) Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol 20:3815–3825
26. Ranson M, Hammond LA, Ferry D, Kris M, Tullo A, Murray PI, Miller V, Averbuch S, Ochs J, Morris C, Feyereislova A, Swaisland H, Rowinsky EK (2002) ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J Clin Oncol 20:2240–2250
27. Patel H, Egorin MJ, Remick SC, Mulkerin D, Takimoto CHM, Doroshow JH, Potter D, Ivy SP, Murgo AJ, Ramanathan RK (2004) Comparison of Child-Pugh criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): implications for chemotherapy dosing. J Clin Oncol ASCO Ann Meet Proc (Post-Meeting Edition) 22:6051
28. Grieco A, Castellano R, Matera A, Marcoccia S, Di Rocco P, Ragazzoni E, Vecchio FM, Gasbarrini G (1998) Antipyrine clearance in chronic and neoplastic liver diseases: a study of 518 patients. J Gastroenterol Hepatol 13:460–466
29. Maring JG, Piersma H, van Dalen A, Groen HJ, Uges DR, De Vries EG (2003) Extensive hepatic replacement due to liver metastases has no effect on 5-fluorouracil pharmacokinetics. Cancer Chemother Pharmacol 51:167–173
30. Koren G, Beatty K, Seto A, Einarson TR, Lishner M (1992) The effects of impaired liver function on the elimination of antineoplastic agents. Ann Pharmacother 26:363–371

31. Dobbs NA, Twelves CJ, Gregory W, Cruickshanka C, Richards MA, Rubens RD (2003) Epirubicin in patients with liver dysfunction: development and evaluation of a novel dose modification scheme. Eur J Cancer 39:580–586
32. Siegel-Lakhai WS, Crul M, De Porre P, Zhang S, Chang I, Boot H, Beijnen JH, Schellens JHM (2006) Clinical and pharmacologic study of the farnesyltransferase inhibitor tipifarnib in cancer patients with normal or mildly or moderately impaired hepatic function. J Clin Oncol 24:4558–4564
33. Shephard CW, Finelli L, Alter MJ (2005) Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 5:558–567