Effects of Smoking on the Pharmacokinetics of Erlotinib

Marta Hamilton, Julie L. Wolf, Jason Rusk, Shannon E. Beard, Gary M. Clark, Karsten Witt, and Pablo J. Cagnoni

Abstract

Purpose: To compare the pharmacokinetic variables of erlotinib in current smokers with nonsmokers after receiving a single oral 150 or 300 mg dose of erlotinib.

Experimental Design: This was a single-center, open-label pharmacokinetic study in healthy male subjects. Subjects were enrolled into two treatment cohorts based on smoking status (current smokers and nonsmokers). The pharmacokinetic profile for erlotinib and its metabolite, OSI-420, was determined for each subject following each treatment.

Results: Current smokers achieved significantly less erlotinib exposure following a single 150 or 300 mg dose than nonsmokers. Following the 150 mg dose, the geometric mean erlotinib AUC_{0-\infty} in smokers was 2.8-fold lower than in nonsmokers and similar to that of nonsmokers at the 300 mg dose. C_{max} in smokers was two-thirds of that in nonsmokers, and C_{24h} in smokers was 8.3-fold lower than in nonsmokers. The median C_{24h} of smokers at the 300 mg dose was slightly less than the C_{24h} of smokers at the 150 mg dose. The median C_{max} was greater in smokers at the 300 mg dose than in nonsmokers at the 150 mg dose.

Conclusion: This study confirms that the pharmacokinetics of erlotinib is different in current smokers and nonsmokers. The observation that AUC_{0-\infty} and C_{24h} were significantly decreased in smokers compared with nonsmokers, and a smaller decrease in C_{max} was observed, is consistent with increased metabolic clearance of erlotinib in current smokers.

Although the recommendation to consider smoking status in clinical studies was made decades ago (1), the effect of smoking on pharmacokinetics has been studied for only a limited number of drugs (2–5). Drugs for which patients’ smoking status may have clinical significance include caffeine (6), chlordiazepoxide (7), chlorpromazine (8), diazepam (7), estradiol (9), flecainide (10, 11), haloperidol (12), heparin (13), imipramine (14), insulin (15), pentazocine (16), propranolol (7), propoxyphene (7), propranolol (17), tacrine (4), and theophylline (18). Studies indicate that some of these drugs, including caffeine, imipramine, pentazocine, tacrine, and theophylline, are likely affected by induction of cytochrome P4501A enzymes.

Erlotinib (Tarceva®, OSI Pharmaceuticals, Melville, NY; Roche, Basel, Switzerland; Genentech, South San Francisco, CA) is an orally active, potent selective inhibitor of the epidermal growth factor receptor tyrosine kinase (19). It is indicated for the treatment of patients with locally advanced or metastatic non–small cell lung cancer after failure of at least one prior chemotherapy regimen and in combination with gemcitabine for the treatment of patients with local advanced, unresectable, or metastatic pancreatic cancer. In the pivotal phase III non–small cell lung cancer trial, BR.21 (20), smoking history was the only factor with a significant and potentially clinically relevant interaction with treatment, indicating that erlotinib was more effective in never smokers than in current or former smokers. Further analyses have also shown that smoking history is a more predictive factor for treatment outcome than epidermal growth factor receptor expression (21, 22).

For the purpose of evaluating erlotinib exposure in BR.21, it made more sense to categorize patients as current versus noncurrent (former or never smokers) given that changes in metabolic enzyme expression are temporally related to the presence of inducers or inhibitors. In BR.21, current smokers had median steady-state erlotinib trough plasma concentrations (C_{24h}) nearly half that of the patients who were noncurrent smokers (23). A possible explanation for this effect is the induction of CYP1A isoforms by cigarette smoke, resulting in faster plasma clearance of erlotinib. Noncurrent smokers also had a higher incidence of adverse events, particularly rash and diarrhea, than patients who continued to smoke, which is consistent with greater erlotinib exposure (23).

Erlotinib is metabolized in the human liver primarily by CYP3A4 but also by CYP1A2 and, to a minor extent, by CYP2C8 (23). Extrathelial metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumor tissue might contribute to the metabolic clearance of erlotinib. The main circulating metabolites of erlotinib are products of O-demethylation of...
either of the side chains, OSI-413 and OSI-420 (Fig. 1). In a study in human male volunteers using \(^{14}\text{C}\)-labeled erlotinib, these two metabolites were found to account for 4.24% and 5.27% of the total circulating radioactivity (24) and generally occur at plasma concentrations of 5% to 10% of that of erlotinib. The in vitro cellular activity against epidermal growth factor receptor is similar in each of these metabolites and to erlotinib. The bioanalytic method employed for the analysis of plasma samples does not distinguish between OSI-413 and OSI-420; therefore, these metabolites are quantified together and collectively referred to in this article as OSI-420.

Because erlotinib is cleared through extensive metabolism, several variables may exist within a given patient that could effect erlotinib exposure. In a population pharmacokinetic analysis (25) of erlotinib exposure in 708 patients from seven clinical studies, patient baseline characteristics, demographics, concomitant administration of cytochrome P450 inducers/ inhibitors, and clinical chemistry variables were tested for their effect on erlotinib exposure. Of the covariates, plasma a-1 acid glycoprotein, total bilirubin, and smoking status were considered to have a significant effect on erlotinib exposure. The magnitude of the effect was the greatest for smoking. The current study was therefore designed to answer a very specific question: Could the decreased erlotinib exposure observed in current smoking cancer patients versus former or never smoking patients in BR.21 be due to their smoking status? If so, could we expect to achieve a proportional increase in erlotinib exposure in current smokers if the dose were doubled?

### Materials and Methods

This study was approved by the institutional review board at MDS Pharma Services (Lincoln, NE) and done in accordance with an assurance filed with and approved by the Department of Health and Human Services.

**Study design and conduct.** This phase I, single-center, open-label, pharmacokinetic crossover study was initiated and sponsored by OSI Pharmaceuticals and conducted by MDS Pharma Services. Subjects had to be healthy males age \(\geq\)19 years, provide verbal and written informed consent, and be willing to abstain from all other prescribed medications, herbal supplements, alcohol, and drugs of abuse during this study. Nonsmokers were subjects who had not consumed tobacco or nicotine-containing products for 1 year before the start of the study. Subjects classified as current smokers must have smoked a minimum of 10 cigarettes per day for \(\geq\)1 year and have a positive test for cotinine.

The erlotinib tablets used in this study contained erlotinib hydrochloride equivalent to 150 mg erlotinib and were manufactured by Schwarz Pharma (Seymour, IN). All subjects were to receive a single dose of 150 mg erlotinib on day 1 followed by a single dose of 300 mg erlotinib on day 15. Tablets were to be taken with up to 200 mL water 1 hour before or 2 hours after meals or milk. Urine cotinine levels were done at baseline and before each erlotinib dose to confirm each subject’s smoking status. Following each single dose erlotinib administration, the subjects stayed in the clinic for at least 48 hours.

**Pharmacokinetic methods.** Eleven plasma sampling times were used to determine the pharmacokinetic profile for each subject (predose, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours) following each dose of erlotinib. Blood samples were collected in tubes containing sodium heparin and centrifuged under refrigeration to obtain plasma. Plasma samples were stored frozen at approximately \(-20^\circ\text{C}\) and were analyzed within 2 months of collection. Studies have shown stability for erlotinib and OSI-420 in plasma stored under these conditions in excess of 1 year. A validated isocratic reverse-phase high-performance liquid chromatography/tandem mass spectrometry method was used for the determination of erlotinib and OSI-420. Diluted buffered plasma fortified with internal standard was loaded on a diatomaceous earth cartridge. A liquid/liquid extraction was done with methyl tertiary butyl ether. Following a dry-down and resuspension, the retained analytes were separated using a Waters Symmetry C-18 column using ammonium formate buffer and methanol as the mobile phase. Erlotinib, OSI-420, and internal standard were eluted from the column, ionized by heated nebulizer, and the mass transitions were monitored at 393.4/277.8, 379.3/277.9, and 407.4/292.1 m/z, respectively. The linear range of the assay is 1 to 600 ng/mL, and the lower limit of quantitation was 1 ng/mL for each analyte. Samples in which concentrations exceeded this range were diluted in control human plasma for analysis. The precision and accuracy of this method was evaluated for the determination of both erlotinib and OSI-420, with accuracy defined as %Bias from nominal and precision as the %CV for replicate sample preparations. For erlotinib, the overall %Bias ranged from \(-1.93\) to 11.2 over the linear range of the assay and the overall %CV ranged from 4.61 to 17.4 (at the lower limit of quantitation). For OSI-420, the overall %Bias in the assay ranged from -0.62 to 8.27 with the overall %CV ranging from 3.72 to 11.2. Additional tests were conducted as per Food and Drug Administration validation guidelines and all fell within acceptable limits (26).

Pharmacokinetic variables were calculated for each subject following each dose using noncompartmental methods (WinNonlin Enterprise version 4.1.0048, Pharsight Corp., Mountain View, CA) and nominal sample times (actual samples times were within 5% of the nominal times). The pharmacokinetic variables included \(C_{\text{max}}, T_{\text{max}}, C_{24\text{h}}, \text{AUC}_{0-\infty}, \text{and } T_{1/2\text{a}}\). The terminal rate constant, \(\lambda_z\), was calculated by using the last three quantifiable time points in each plasma profile. \(\text{AUC}_{0-\infty}\) was calculated by the log-linear trapezoidal rule and extrapolated to infinite time using the relationship: \[ \text{AUC} \text{extrapolated} = C_{\text{sam}}/\lambda_z \]

Plasma concentrations that were below the lower limit of quantitation were treated as missing values.

**Statistical analysis methods.** For the assessment of a smoking effect following the 150 mg dose, Student’s \(t\) tests on log-transformed data were conducted to test for differences in \(\text{AUC}_{0-\infty}, C_{\text{max}}, \text{and } C_{24\text{h}}\) between smokers and nonsmokers. The \(P\) for the difference between smoking and nonsmoking geometric means was reported and deemed significant if \(\leq 0.05\). Ninety-five percent confidence intervals (95% CI) for the ratios of geometric means were calculated to characterize the effect due to smoking as well as the effect due to doubling the erlotinib dose from 150 to 300 mg.

**Safety assessment.** Safety was evaluated for all subjects by assessing treatment-emergent adverse events, clinical laboratory results, and vital signs.
Results

Demographics. Thirty-two male subjects were enrolled, 16 subjects in each cohort. The mean ages were 31 years (range, 19-52) and 39 years (range, 19-54), respectively, in the nonsmoker and smoker cohorts. All but 2 subjects in each cohort were Caucasian.

Subject compliance. The majority of subjects (12 nonsmokers and 14 smokers) completed the study. Six subjects did not receive the day 15 dose of erlotinib. Five subjects (3 nonsmokers and 2 smokers) were discontinued from the study due to noncompliance and 1 nonsmoker requested to withdraw from the study due to a family emergency.

Pharmacokinetics. Erlotinib and OSI-420 pharmacokinetic variable summary statistics are presented in Table 1. A comparison of the median concentrations of erlotinib observed over the 72-hour plasma sampling time following the 150 mg erlotinib dose and the 300 mg erlotinib dose is presented in Fig. 2.

Plasma concentrations of erlotinib and OSI-420 appeared rapidly in both nonsmokers and smokers (median $T_{\text{max}}$ of 2 hours in both cohorts); however, both analytes were eliminated more rapidly in smokers than in nonsmokers. These analyses indicate that individuals who smoke have an increased clearance and a decreased exposure to erlotinib.

Pharmacokinetics of erlotinib and OSI-420 following the 150 mg dose. Student's $t$ tests and 95% CI were calculated for the ratio of the geometric means of nonsmokers and smokers for $C_{\text{max}}$, AUC$_{0-1}$, and $C_{24h}$. The geometric mean of the erlotinib $C_{\text{max}}$ was 1,056 ng/mL in nonsmokers and 689 ng/mL in smokers with a mean ratio for smokers to nonsmokers of 65.2% (95% CI, 44.3-95.9; $P = 0.031$). The geometric mean of

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Dose (mg)</th>
<th>Erlotinib</th>
<th>OSI-420</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$T_{\text{max}}$ (h)</td>
<td>$C_{24h}$ (ng/mL)</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>150 (n = 16)</td>
<td>Median</td>
<td>1,055 2</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>655 1</td>
<td>71.2 8,259</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>1,470 6</td>
<td>489 28,766</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1,056 288</td>
<td>18,726</td>
<td>67.9 14.5</td>
</tr>
<tr>
<td></td>
<td>300 (n = 12)</td>
<td>Median</td>
<td>2,085 2</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>1,300 1</td>
<td>374 25,352</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2,750 4</td>
<td>1,610 85,753</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1,979 776</td>
<td>44,317</td>
<td>143 46.4</td>
</tr>
<tr>
<td>Smokers</td>
<td>150 (n = 16)</td>
<td>Median</td>
<td>950 2</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>124 1</td>
<td>1.25 1,005</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>1,360 6</td>
<td>228 15,325</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>689 34.8</td>
<td>6,718</td>
<td>41.2 4.41</td>
</tr>
<tr>
<td></td>
<td>300 (n = 14)</td>
<td>Median</td>
<td>1,795 2</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>632 1</td>
<td>35.1 9,029</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2,730 8</td>
<td>479 29,701</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1,577 229</td>
<td>19,050</td>
<td>102 12.8</td>
</tr>
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</table>

Fig. 2. Erlotinib concentrations versus time following the 150 mg erlotinib dose (A) and the 300 mg erlotinib dose (B). The AUC$_{0-1}$ (ng/h/mL) of the smokers was approximately half that of the nonsmokers (ratio of smokers/nonsmokers at 150 mg = 35.9; ratio at 300 mg = 43.0). The effect on $C_{\text{max}}$ (ng/mL) was smaller (ratio of the smokers/nonsmokers at 150 mg = 65.2; ratio at 300 mg = 79.7).
the erlotinib AUC\textsubscript{0-$\infty$} was 18,726 ng\cdot h/mL in nonsmokers and 6,718 ng\cdot h/mL in smokers with a mean ratio of 35.9\% (95\% CI, 23.7-54.3; \( P < 0.0001 \)). The geometric mean of the erlotinib \( C_{24h} \) was 288 ng/mL in nonsmokers and 34.8 ng/mL in smokers with a mean ratio of 12.1\% (95\% CI, 4.82-30.2; \( P = 0.0001 \)).

Similar to the observations from the erlotinib data, current smokers had lower OSI-420 exposure than their nonsmoking counterparts. The geometric mean of the OSI-420 \( C_{\text{max}} \) was 67.9 ng/mL in nonsmokers and 41.2 ng/mL in smokers with a mean ratio of 60.7\% (95\% CI, 41.0-89.9). The geometric mean of the OSI-420 AUC\textsubscript{0-$\infty$} was 1,037 ng\cdot h/mL in nonsmokers and 469 ng\cdot h/mL in smokers with a mean ratio of 45.3\% (95\% CI, 30.0-68.3). The geometric mean of the OSI-420 \( C_{24h} \) was 14.5 ng/mL in nonsmokers and 4.41 ng/mL in smokers with a mean ratio of 30.5\% (95\% CI, 18.5-50.2).

**Pharmacokinetics of erlotinib following the 300 mg dose.**

Nonsmokers also had higher concentrations of erlotinib and slower apparent clearance than smokers with the 300 mg erlotinib dose administered on day 15. Six subjects did not receive the day 15 dose of 300 mg erlotinib. Table 2 presents the geometric mean ratios of 300 to 150 mg for the \( AUC_{0-$\infty$} \), \( C_{\text{max}} \), and \( C_{24h} \) to further characterize the effect of escalating the dose of erlotinib in each cohort based on subjects who received erlotinib doses on both day 1 (150 mg) and day 15 (300 mg).

The geometric mean ratio of 300 to 150 mg for each of the variables for erlotinib was higher for smokers than nonsmokers, although the 95\% CIs overlapped in all calculations, suggesting dose-proportional exposure in both cohorts. The greatest difference between the cohorts was observed in \( C_{24h} \) in which nonsmokers had a geometric mean ratio of 247\% and smokers had a higher ratio of 565\%. The geometric mean ratios for \( C_{\text{max}} \) and \( C_{24h} \) for OSI-420 generated similar values between nonsmokers and smokers. The geometric mean ratios for AUC\textsubscript{0-$\infty$} for OSI-420 were higher in nonsmokers than smokers.

The median erlotinib plasma concentrations in nonsmokers following the 150 mg erlotinib dose compared with smokers following the 300 mg erlotinib dose are shown in Fig. 3. The median erlotinib AUC\textsubscript{0-$\infty$} in nonsmokers at the 150 mg dose was similar to that of smokers at the 300 mg dose, 20,577 versus 19,676 ng\cdot h/mL, respectively. Similarly for OSI-420, the AUC\textsubscript{0-$\infty$} in nonsmokers at the 150 mg dose versus smokers at the 300 mg dose was 1,102 ng\cdot h/mL compared with 1,179 ng\cdot h/mL. The median erlotinib \( C_{24h} \) in nonsmokers at the 150 mg dose was 332 ng/mL, slightly higher than the \( C_{24h} \) (259 ng/mL) of smokers at the 300 mg dose. The median erlotinib \( C_{\text{max}} \) was lower in nonsmokers at the 150 mg dose than in smokers at the 300 mg dose, 1,055 versus 1,795 ng/mL.

**Safety evaluation.** Ten subjects (3 nonsmokers and 7 smokers) reported adverse events during the 150 mg dose period and 11 subjects (3 nonsmokers, 8 smokers) reported adverse events in the 300 mg dose period. The only adverse events reported by \( \geq 3 \) subjects were headache (most at the 150 mg dose), loose stools and fatigue (both only in smokers), and nausea. Most adverse events were considered related to erlotinib and were of mild severity. One serious adverse event occurred in which a subject developed severe gastroenteritis, considered unrelated to erlotinib, 12 days after receiving the day 1 (150 mg) erlotinib dose.

No meaningful differences were observed in safety between the nonsmoking cohort and the smoking cohort or between the 150 mg and the 300 mg erlotinib doses.

**Discussion**

This study was designed to answer a very specific question: Can cigarette smoking decrease exposure to erlotinib? Because

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**Table 2. Geometric mean ratios and 95\% CIs for each cohort for the ratio of 300 to 150 mg pharmacokinetic variables for erlotinib and OSI-420**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Pharmacokinetic variable</th>
<th>Nonsmokers</th>
<th></th>
<th>Nonsmokers</th>
<th></th>
<th>Smokers</th>
<th></th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>( AUC_{0-$\infty$} )</td>
<td>12</td>
<td>226.1 (176.0-290.3)</td>
<td>14</td>
<td>250.0 (173.4-360.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max}} )</td>
<td>12</td>
<td>190.1 (153.6-235.4)</td>
<td>14</td>
<td>204.1 (134.3-310.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( C_{24h} )</td>
<td>12</td>
<td>247.2 (185.3-329.8)</td>
<td>14</td>
<td>565.0 (208.3-1532.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSI-420</td>
<td>( AUC_{0-$\infty$} )</td>
<td>12</td>
<td>241.7 (172.9-338.1)</td>
<td>14</td>
<td>219.8 (150.4-321.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max}} )</td>
<td>12</td>
<td>218.1 (164.8-288.7)</td>
<td>14</td>
<td>218.2 (140.5-338.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( C_{24h} )</td>
<td>12</td>
<td>292.5 (206.3-414.7)</td>
<td>12</td>
<td>289.7 (164.0-511.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
the study was designed to isolate this variable for testing, a very homogeneous population was chosen for testing.

Results from this study confirmed that the pharmacokinetics of erlotinib and OSI-420 are different in smokers than in nonsmokers. Erlotinib exposure, as measured by AUC_{0-∞}, C_{max} and C_{24h}, were significantly decreased in smokers compared with nonsmokers. These results are not unexpected given the known contribution of CYP1A1 and CYP1A2 to the metabolism of erlotinib and their induction by cigarette smoking. The metabolic products of these reactions, however, are not unique to the CYP1A enzymes and are also produced through CYP3A4 catalyzed reactions. Their presence or extent of formation, although consistent with this hypothesis, cannot be used to definitely prove that the observed increased clearance of erlotinib is through this mechanism.

Erlotinib plasma concentrations were significantly decreased in smokers in this study presumably due to increased metabolism of erlotinib; however, concentrations of a main metabolite, OSI-420, were not increased. To the contrary, similar decreases in OSI-420 were observed in smokers, which is not necessarily inconsistent with the proposed hypothesis of enzyme induction, as studies have shown that OSI-420 is further metabolized in vivo (23, 24). Other pathways of erlotinib metabolism, shown to be catalyzed by CYP1A enzymes, such as aniline phenyl hydroxylation and oxidation of the acetylene group, may also be induced under these conditions but could not be monitored in this study (and as noted above, can also be produced through CYP3A4-mediated reactions). The bioanalytic method was not validated for these other metabolites based on the results from the radiolabeled mass balance study in humans (24), which indicated that erlotinib, OSI-413, and OSI-420 were the primary species observed in plasma. A total of 17 metabolites (combinations of oxidation products, including conjugates) were identified in this study, primarily in feces.

Interestingly, the rate of elimination in individual smokers seemed to increase with decreasing plasma concentrations, which was minimal to nonexistent in the plasma profiles from the nonsmoker cohort. An example of this can be seen in the elimination rate profile of an individual nonsmoking subject and a smoking subject (Fig. 4). This observation was consistent for both analytes following both 150 and 300 mg doses and suggests a greater contribution of a saturable clearance pathway in smokers compared with nonsmokers. Similar nonlinear pharmacokinetic elimination was observed in nonclinical studies with erlotinib but had not been typical of the experience to date with erlotinib pharmacokinetics in humans.

In conclusion, this study supports that the decrease in erlotinib exposure observed in current smoking non–small cell lung cancer patients in BR.21 could be due to their smoking status and that an increased dose of erlotinib may benefit these patients. Studies using higher erlotinib doses in non–small cell lung cancer patients have been initiated. If greater doses of erlotinib are shown to improve the treatment outcome in current smokers, consideration should also be given to how patients exposed to secondhand smoke are dosed. The results of this study also highlight the need for collection of accurate smoking history in all studies of drugs for which smoking-related effects on metabolism are suspected.

**References**

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