Published in final edited form as:

Cancer Chemother Pharmacol. 2015 October ; 76(4): 813–819. doi:10.1007/s00280-015-2856-y.

Preclinical assessment of the interactions between the antiretroviral drugs, ritonavir and efavirenz, and the tyrosine kinase inhibitor erlotinib

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Abstract

Purpose—Prevalence of non-AIDS-defining cancers (NADCs) has increased in the era of potent antiretroviral treatments. Incidence rates of NADCs now exceed AIDS-defining cancers in HIV-positive patients. Treatment of NADCs may be complicated by interactions between antiretrovirals and chemotherapy mostly via inhibition or induction of CYP3A4. Erlotinib is used to treat non-small cell lung and pancreatic cancer and is primarily metabolized by CYP3A4 into multiple products including the active metabolite (OSI-420). Preclinical in vivo assessment was performed to gain a better understanding of CYP3A4-mediated interactions between antiretrovirals and erlotinib.

Methods—Erlotinib (50 mg/kg p.o.) was administered to male FVB mice in the presence and absence of dexamethasone (10 mg/kg p.o. QDx4), efavirenz (25 mg/kg p.o. QDx4), ketoconazole (50 mg/kg p.o.), or ritonavir (12.5 mg/kg p.o.). Blood samples were collected to characterize exposure (AUC).

Results—Administration of erlotinib with CYP3A4 inducers (dexamethasone) and inhibitors (ketoconazole and ritonavir) resulted in significant alterations in erlotinib exposure. Ketoconazole and ritonavir resulted in a 1.7- and 3.0-fold increase in erlotinib AUC, respectively, while

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Compliance with ethical standards

Conflict of interest None.

dexamethasone results in a 0.6-fold decrease in erlotinib AUC. The CYP3A4 inducer efavirenz did not have a significant effect on erlotinib exposure.

Conclusion—CYP3A4 inducers and inhibitors altered the exposure of erlotinib. Until a definitive clinical trial is performed, erlotinib should be used with caution in patients on a ritonavir-containing antiretroviral regimen, while standard doses may be appropriate for patients on an efavirenz-containing antiretroviral regimen.

Keywords

Erlotinib; Drug interaction; AIDS; Ritonavir; Efavirenz

Introduction

With the advent of combination antiretroviral therapy (cART) in the late 1990s, HIV infection has changed from being a fatal diagnosis to a chronic, manageable illness. The morbidity and mortality from HIV have been reduced dramatically, including the rates of AIDS-defining cancers of non-Hodgkin's lymphoma, Kaposi's sarcoma, and cervical cancer [1]. Unfortunately, epidemiology research over the past decade has shown that patients with HIV are now being diagnosed with cancers not previously associated with HIV, such as lung, head and neck, liver, anal, and kidney cancers, at much higher rates than the general population for reasons that are not yet understood [2]. The incidence of non-AIDS-defining cancers (NADCs) has been on the rise and has in fact increased more than threefold, now surpassing the incidence of AIDS-defining malignancies in HIV-infected individuals [3]. In the postc-ART era, lung cancer rates among HIV-positive patients have increased, and the risk of HIV-positive patients being diagnosed with lung cancer is between 2 and 6 times that seen in HIV-negative patients, including after stratifying risk based on tobacco use [1, 2, 4–6]. Further, lung and other solid tumors seen at higher rates in HIV-positive patients typically occur at an earlier age, have poor prognosis features and histologies, metastasize more readily and earlier, and carry a worse prognosis in terms of survival [2]. How best to treat HIV patients on cART therapy for these NADCs is an emerging critical challenge facing medical oncology.

Recommendations of optimal antiretroviral regimen consist of a combination of two nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third active antiretroviral drug from one of the three categories: non-nucleoside reverse transcriptase inhibitors (NNRTIs), ritonavir-boosted protease inhibitors (PIs) or an integrase strand transfer inhibitor (INSTI) [7]. Comorbidities, viral mutations, drug–drug interaction potential, and tolerance of drug regimens all play a major role in the selection of the right cART regimen for an individual patient [7]. Drug–drug interactions are prevalent with antiretrovirals since most are substrates, inducers, and/or inhibitors of drug-metabolizing isozymes, including cytochrome P450 (CYP450) and uridine diphosphate glucuronyl transferases (UGT), as well as drug efflux and uptake transporters [8–10]. Ritonavir is most commonly recognized and utilized as a potent inhibitor of CYP3A4 in “boosted” cART regimens despite having differential effects on various isozymes [9–11]. Additionally, the antiretroviral efavirenz has mixed CYP3A4 inhibition/induction potential but clinically results in enzyme induction [12–14].

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) approved by the FDA for treatment of advanced non-small cell lung cancer, as a single agent, and advanced pancreatic cancer in combination with gemcitabine. Somatic mutations in the EGFR gene in exon 19 (exon19del) and exon 21 (L858R) activate the tyrosine kinase domain of EGFR and are sensitive to the inhibitory effects of erlotinib and similar EGFR tyrosine kinase inhibitors [15]. Such EGFR mutations are found in about 10 % of Caucasian patients and up to 50 % of Asian patients [16]. Yet, the only published case series on mutations detected in HIV-positive patients found that two of seven patients (29 %) had mutations in EGFR [17].

The utility of erlotinib in HIV-positive patients specifically has not been thoroughly examined due to the concerns of drug–drug interactions. Indeed, erlotinib is primarily metabolized by cytochrome P450 3A4 (CYP3A4) into multiple products, including an active O-desmethyl metabolite (OSI-420), and is susceptible to drug–drug interactions, especially via inhibition or induction of CYP3A4 and CYP1A2 [18]. Currently, it is recommended to avoid the use of erlotinib with a potent inhibitor or a potent inducer, which is further supported by hepatocyte data which demonstrated a 16-fold decrease by ritonavir and a 2.2-fold increase by efavirenz in apparent intrinsic clearance of erlotinib [19, 20]. Erlotinib is a known substrate for ABCB1 and ABCG2 [21].

We sought to elucidate whether a mouse model to assess drug–drug interactions would result in similar alterations in erlotinib exposure as predicted from the hepatocyte method. Ketoconazole was selected as the “index” CYP3A4 inhibitor. Dexamethasone was selected as the more potent inducer of CYP3A4 compared to rifampicin with weak induction effect on other CYP450s and ABCB1 [22–24]. Efavirenz and ritonavir were selected as the strongest inducer and inhibitor of CYP3A4 among the antiretrovirals that are commonly utilized in clinical practice. In this study, we conducted an in vivo assessment of the pharmacokinetics of erlotinib administered orally when co-administered with CYP3A4 inhibitors or inducers in mice.

Methods

Chemicals and reagents

Erlotinib and OSI-420 were obtained from Toronto Research Chemicals (North York, ON, Canada). Drug-free (blank) mouse plasma was obtained from Innovative Research, Inc. (Novi, MI). cART agents were commercially available and of pharmaceutical grade. All other chemicals and reagents were of the highest grade commercially available.

Erlotinib pharmacokinetics in combination with CYP3A4 inducers or inhibitors

Male FVB mice (6 weeks old, Taconic, Germantown, NY) were maintained in a controlled environment with food and sterilized water available ad libitum. Animal experimentation was conducted under an approved Institutional Animal Care and Use Committee (IACUC) protocol in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited facility and complied with local and national guidelines. Erlotinib was formulated in 0.3 % (w/v) carboxymethylcellulose and 0.1 % (v/v) polysorbate 80 (Tween 80) to a final concentration of 5 mg/mL. Dose formulation was sonicated for 5 min

and vortex-mixed for 5–10 min prior to administration. Erlotinib was administered in the presence and absence of dexamethasone, efavirenz, ketoconazole, or ritonavir by oral gavage at a dose of 50 mg/kg [25, 26]. Dexamethasone and efavirenz were administered by oral gavage daily for 4 days with the last dose occurring approximately 45 min prior to erlotinib administration to ensure CYP3A4 induction. Dexamethasone was administered at a dose of 10 mg/kg, while efavirenz was administered at a dose of 25 mg/kg. Ketoconazole and ritonavir were administered by oral gavage at a dose of 50 mg/kg and 12.5 mg/kg, respectively, at approximately 1 h prior to erlotinib administration to ensure adequate CYP3A4 inhibition [27]. Blood samples were collected by cardiac puncture from three mice per time point into syringes coated with heparin as a function of time following erlotinib administration and centrifuged immediately to obtain plasma. Plasma samples were stored in a liquid nitrogen freezer until analysis. A validated LC–MS–MS method was used to quantitate erlotinib plasma concentrations over the range of 5–5000 ng/mL and OSI-420 over the range of 1–1000 ng/mL, and dilutions up to 1:10 (v/v) were accurately quantitated [28].

Pharmacokinetic parameters were calculated from mean concentration–time data using non-compartmental methods as analyzed in Phoenix[®] WinNonlin[®] version 6.3 (Pharsight A Certara[™] Company, Cary, NC). $C_{\max}$ was the observed value. The AUC_{last} was calculated using the linear trapezoidal method and extrapolated to infinity ($AUC_{0-\infty}$) by dividing the last quantifiable concentration by the terminal disposition rate constant (λ_z). The λ_z was determined from at least three points on the slope of the terminal phase of the concentration–time profile with a weighting factor of $1/y$. The terminal half-life ($T_{1/2}$) was determined by dividing 0.693 by λ_z . Oral apparent clearance (Cl/F) was calculated by dividing the dose administered by $AUC_{0-\infty}$. If the percent AUC extrapolated was >25 % or the r^2 of λ_z was <0.9, the $AUC_{0-\infty}$, Cl/F, and $T_{1/2}$ were not reported.

Statistical analysis

A Kruskal–Wallis analysis of variance test was used to compare the individual $C_{\max}$ values at the average $T_{\max}$ with a Tukey–Kramer HSD post hoc analysis. Method of Bailer was used to estimate the variance of AUC given the calculated variance of the mean concentration at each time point [29]. A pairwise comparison using Z test was used to determine whether there was a significant difference between erlotinib exposures as expressed by AUC_{last} [30]. In all cases, $p < 0.05$ was considered statistically significant.

Results

Erlotinib was administered to mice in the presence or absence of CYP3A4 inducers (Fig. 1) or inhibitors (Fig. 2) to determine the extent of alterations in the pharmacokinetic profile of erlotinib. Erlotinib demonstrated an erratic absorption pattern which is consistent with previous reports on murine pharmacokinetics [25, 26]. Due to this erratic pattern, the half-life and oral apparent clearance were not consistently estimated across all experimental conditions and therefore is not discussed. Erlotinib concentrations were detectable up to 18 h for control arm and up to 24 h for all other treatment arms. OSI-420 concentrations were

detectable up to 10 h for control arm, 18 h for dexamethasone, efavirenz, and ketoconazole arms, and 24 h for ritonavir arm.

Administration with CYP3A4 inducers or inhibitors resulted in alterations in exposure of erlotinib and OSI-420 (Table 1). The maximal exposure ($C_{\max}$) of erlotinib was statistically different (Kruskal–Wallis ANOVA $p = 0.049$). However, only dexamethasone had significantly lower concentrations compared to ritonavir with post hoc analysis. There was no observed difference in the OSI-420 $C_{\max}$ (Kruskal–Wallis ANOVA $p = 0.13$). The presence of dexamethasone resulted in a 39 % decrease (45.6 vs. 74.8 $\mu\text{g h/mL}$; $p = 0.013$), while efavirenz resulted in a 17 % decrease (62.2 vs. 74.8 $\mu\text{g h/mL}$; $p = 0.10$) in erlotinib AUC_{last} . There was no alteration in OSI-420 AUC_{last} when erlotinib was administered with dexamethasone (27.6 vs. 22.0 $\mu\text{g h/mL}$; $p = 0.15$) or efavirenz (20.3 vs. 22.0 $\mu\text{g h/mL}$; $p = 0.62$). The co-administration of ketoconazole, a control CYP3A4 inhibitor, resulted in a 73 % increase (129.0 vs. 74.8 $\mu\text{g h/mL}$; $p < 0.0001$), while ritonavir resulted in a 205 % increase (227.9 vs. 74.8 $\mu\text{g h/mL}$; $p < 0.0001$) in erlotinib AUC_{last} . There was no alteration in OSI-420 AUC_{last} when erlotinib was administered with ritonavir (30.3 vs. 22.0 $\mu\text{g h/mL}$; $p = 0.093$) or ketoconazole (13.4 vs. 22.0 $\mu\text{g h/mL}$; $p = 0.006$). Dexamethasone was a more potent inducer of erlotinib elimination than efavirenz, while ritonavir was a more potent inhibitor of erlotinib elimination than ketoconazole. The metabolic ratio of erlotinib to OSI-420 was 0.29 for control, 0.61 for dexamethasone, 0.33 for efavirenz, 0.10 for ketoconazole, and 0.13 for ritonavir.

Discussion

This study demonstrates that oral administration of the antiretroviral CYP3A4 inhibitor ritonavir significantly altered the systemic erlotinib exposure after oral administration of erlotinib, but the antiretroviral CYP3A4 inducer efavirenz did not. The magnitude of the interaction with ritonavir (3.05-fold or 205 % increase in AUC_{last}) was benchmarked against the prototypical CYP3A4 inhibitor ketoconazole (1.73-fold or 73 % increase in AUC_{last}), demonstrating that ritonavir is a more potent CYP3A4 inhibitor. The only significant change in $C_{\max}$ was between dexamethasone and ritonavir. The major alteration in erlotinib exposure is in total (AUC_{last}) rather than maximal ($C_{\max}$) exposure, which suggests that the effect is not solely reliant on the first-pass metabolism. The alterations to OSI-420 were less pronounced, suggesting that other metabolic routes such as CYP1A2 or CYP2C8 may have compensated for the differences in the parent drug or that bioavailability of erlotinib was increased. The metabolic fate of OSI-420 has only been attributed to CYP3A4 in the literature, albeit other CYP450 s may be involved further confounding the results [31]. It should also be noted that the metabolite/parent drug ratio of ~29 % for the control arm is similar to prior experiments utilizing mice [25] but is still fivefold higher than that reported in the mass balance study and human hepatocyte experiment [19, 31]. Therefore, the alterations noted in mice may not be reflective of humans. Due to the differential alteration in erlotinib and OSI-420 individually, the metabolite/parent drug ratio was changed by a different magnitude (i.e., ritonavir caused a 3.05-fold or 205 % increase in erlotinib exposure, and 1.38-fold or 38 % increase in OSI-420 exposure with a net decrease of 0.45-fold or 55 % decrease in the ratio).

Our findings are generally consistent with the CYP3A4 inhibition literature [19, 31]. The 1.7-fold increase in erlotinib exposure when administered with ketoconazole is consistent with the 1.9-fold decrease in predicted human erlotinib CL_{oral} observed in hepatocytes [19] and a twofold increase in erlotinib exposure in a healthy volunteer trial that was predicted by SimCYP™ [31]. However, the alteration by the CYP3A4 inhibitor ritonavir was substantially reduced (threefold) compared with the 16-fold decrease in predicted human erlotinib CL_{oral} observed in hepatocytes [19]. The reason for the difference with ritonavir may be due to the assumption that the fraction of dose escaping gut wall metabolism was 100 % [19], whereas both the hepatocyte data and the SimCYP™ data assumed that the bioavailability was 100 % [19, 31]. The dose of ritonavir was previously shown not to induce or inhibit Cyp3a11 or Abcb1a in mouse liver, which would be consistent with the low-dose regimens commonly utilized in cART [27].

Our findings are less significant than those seen with CYP3A4 induction [19, 32]. We did not utilize the same control CYP3A4 inducer of rifampicin; therefore, a direct comparison could not be made. We selected dexamethasone which is a known potent inducer of CYP3A4 with weak induction effect on the other CYP450 s and ABCB1 [22, 23]. Rifampicin, which is the prototypical CYP3A4 inducer, can also induce ABCB1 and inhibits some OATPs [33]. While the direction of the alteration in erlotinib exposure is similar when administered with dexamethasone or rifampicin, the magnitude is not consistent (0.6-fold decrease with dexamethasone compared to the 0.3-fold decrease in hepatocytes [19] or healthy volunteers when combined with rifampicin [32]). The alteration by the CYP3A4 inducer efavirenz did not reach statistical significance, which is different than the 2.2-fold increase in predicted human erlotinib CL_{oral} observed in hepatocytes [19]. As with the CYP3A4 inhibition, the direction of the interaction was consistent, but the magnitude was less.

Based on the results of our in vivo study and the previous in vitro hepatocyte study [19], one would anticipate that standard erlotinib dosing would not be tolerable in patients receiving ritonavir-based cART. This has prompted the AIDS Malignancy Consortium to design a prospective clinical trial determining the actual dose in AIDS patients on cART (Clinicaltrials.gov, NCT02134886). Since erlotinib is not a cytotoxic agent and has minimal serious adverse effects associated with exposure, the dose selection tended more toward the FDA-approved doses. The primary objective of this trial will be to determine the safety, tolerability, and maximum tolerated dose of single-agent erlotinib in non-small cell lung cancer participants with HIV receiving cART. Based on the hepatocyte study, with a 16-fold decrease in predicted CL_{oral} , the starting dose was suggested to be 25 mg every other day. Our current study suggests a 3.0-fold increase in exposure, and one would also anticipate a less drastic reduction in dose to 50–100 mg daily [20]. The lack of effect of efavirenz co-administration on erlotinib exposure is suggestive that a standard dose would be tolerable in patients receiving a cART regimen containing efavirenz. When designing the clinical trial in HIV patients on cART, the starting doses were selected to be more in line with the suggested prescribing information, which recommends avoiding strong inhibitors if possible with implementation of 50 mg dose reductions based on tolerability if not possible [20]. Therefore, the starting dose in the CYP3A4 inhibiting stratum in the ongoing AIDS Malignancy Consortium trial is 100 mg of erlotinib daily with an increase to the FDA-

approved dose of 150 mg. Since the CYP3A4 induction did not appear to be pronounced, the starting dose in the CYP3A4 inducing stratum is 150 mg and allows for intra-patient dose escalation based on tolerance up to a maximum dose of 450 mg. The confirmatory phase I dose-finding trial of erlotinib in combination with cART through the AIDS Malignancy Consortium will provide definitive recommendations for treating physicians.

Acknowledgments

This work is funded by contract N02-CM-62212. The project described was supported by the Analytical Pharmacology Core of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (NIH Grants P30 CA006973 and UL1 TR 001079, and Shared Instrument Grant 1S10RR026824-01) and Cancer Pharmacokinetics and Pharmacodynamics Facility at University of Pittsburgh Cancer Institute (P30 CA047904). Grant Number UL1 TR 001079 is from the National Center for Advancing Translational Sciences (NCATS), a component of the NIH, and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins ICTR, NCATS, or NIH.

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Fig. 1.

Erlotinib (a) and metabolite (b) plasma concentration–time curves following administration alone or within 1 h after four doses of CYP3A4 inducers to male FVB mice. Erlotinib was administered at a dose of 50 mg/kg, p.o. Dexamethasone (10 mg/kg, p.o.) and efavirenz (25 mg/kg, p.o.) were the CYP3A4 inducers. Data points and *error bars* represent the mean and standard deviation of three points, respectively

Fig. 2. Erlotinib (a) and metabolite (b) plasma concentration–time curves following administration alone or within 1 h after a single dose of CYP3A4 inhibitors to male FVB mice. Erlotinib was administered at a dose of 50 mg/kg, p.o. Ketoconazole (50 mg/kg, p.o.) and ritonavir (12.5 mg/kg, p.o.) were the CYP3A4 inhibitors. Data points and error bars represent the mean and standard deviation of three points, respectively

Table 1

Erlotinib or OSI-420 plasma pharmacokinetic parameters after erlotinib administration in combination with CYP3A4 inducers and inhibitors

Erlotinib	Control	+ Dexamethasone	+ Efavirenz	+ Ketoconazole	+ Ritonavir
Erlotinib					
$T_{\max}$ (h)	0.25	0.25	6	0.5	8
$C_{\max}$ ($\mu\text{g/mL}$) ^b	17.4 $\pm$ 4.7	9.0 $\pm$ 1.0*	13.6 $\pm$ 2.4	14.8 $\pm$ 4.7	21.2 $\pm$ 36.9*
Fold change	–	0.52	0.78	0.85	1.22
AUC _{0–t} ($\mu\text{g} \times \text{h/mL}$) ^c	74.8*, [§]	45.6*	62.2	129.0 ⁺	227.9 [§]
Fold change	–	0.61	0.83	1.73	3.05
$T_{1/2}$ (h)	0.7	4.9	N.R. ^a	3.5	N.R. ^a
Cl/F (L/h/kg)	0.67	0.97	N.R. ^a	0.36	N.R. ^a
Fold change	–	1.46	N.R.	0.54	N.R.
OSI-420					
$T_{\max}$ (h)	1	0.25	6	8	10
$C_{\max}$ ($\mu\text{g/mL}$)	3.3 $\pm$ 0.7	3.8 $\pm$ 0.8	3.5 $\pm$ 0.8	1.4 $\pm$ 0.1	3.9 $\pm$ 1.4
Fold change	–	1.13	1.04	0.41	1.16
AUC _{0–t} ($\mu\text{g} \times \text{h/mL}$)	22.0	27.6	20.3	13.4	30.3
Fold change	–	1.26	0.92	0.61	1.38
$T_{1/2}$ (h)	N.R. ^a	3.6	N.R. ^a	N.R. ^a	N.R. ^a
OSI-420:erlotinib					
AUC _{0–t} ratio	0.29	0.61	0.33	0.10	0.13
Fold change	–	2.06	1.11	0.35	0.45

AUC_{0–∞}, area under the concentration–time curve extrapolated to infinity; $C_{\max}$ maximum concentration, terminal $T_{1/2}$ terminal half-life, $T_{\max}$ time to maximum concentration

^aNot reported due to >25 % extrapolation of the AUC or the r^2 of λ_z was <0.9

^bKruskal–Wallis significantly different. The treatments that are different ($p < 0.05$) with post hoc analysis are denoted with an asterisk

^cMethod of Bailer was significantly different. The treatments that are different ($p < 0.05$) utilizing a Z test are denoted with different symbols