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Dovitinib and erlotinib in patients with metastatic non-small cell lung cancer: A drug–drug interaction

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ABSTRACT

Introduction: Erlotinib is a FDA approved small molecule inhibitor of epidermal growth factor receptor and dovitinib is a novel small molecule inhibitor of fibroblast growth factor and vascular endothelial growth factor receptor. This phase 1 trial was conducted to characterize the safety and determine the maximum tolerated dose of erlotinib plus dovitinib in patients with previously treated metastatic non-small cell lung cancer.
Methods: Escalating dose cohorts of daily erlotinib and dovitinib dosed 5 days on/2 days off, starting after a 2-week lead-in of erlotinib alone, were planned. A potential pharmacokinetic interaction was hypothesized as dovitinib induces CYP1A1/1A2. Only cohort 1 (150 mg erlotinib + 300 mg dovitinib) and cohort -1 (150 mg erlotinib + 200 mg dovitinib) enrolled. Plasma concentrations of erlotinib were measured pre- and post-dovitinib exposure.
Results: Two of three patients in cohort 1 had a DLT (grade 3 transaminitis and grade 3 syncope). Two of 6 patients in cohort -1 had a DLT (grade 3 pulmonary embolism and grade 3 fatigue); thus, the study was terminated. Erlotinib exposure (average C_{max} 2308 ± 698 ng/ml and AUC $_{0-24}$ 41,030 ± 15,577 ng × h/ml) approximated previous reports in the six patients with pharmacokinetic analysis. However, erlotinib C_{max} and AUC_{0-24} decreased significantly by 93% ($p = 0.02$) and 97% ($p < 0.01$), respectively, during dovitinib co-administration.
Conclusions: This small study demonstrated considerable toxicity and a significant pharmacokinetic interaction with a marked decrease in erlotinib exposure in the presence of dovitinib, likely mediated through CYP1A1/1A2 induction. Given the toxicity and the pharmacokinetic interaction, further investigation with this drug combination will not be pursued.

1. Introduction

Erlotinib, afatinib, and gefitinib are epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) that are effective in treating non-small cell lung cancer (NSCLC) patients with known EGFR activating mutations, with response rates (RRs) of ~60–70% and a significant improvement in progression-free survival (PFS) when compared with platinum-based chemotherapy. Unfortunately, resistance develops in the majority of patients in less than 1 year. [1–3] In unselected patients, RRs are very low with EGFR TKIs, but PFS and overall survival (OS) benefits have been documented when compared to placebo in the refractory setting. [4] Exploration of strategies to improve the efficacy of these agents in patients without EGFR activating mutations, to delay development of resistance in those with EGFR activating mutations, and to overcome resistance once it develops is critical. One such approach is to combine EGFR TKIs with other targeted agents, in particular those targeting angiogenesis via the vascular endothelial growth factor (VEGF)/VEGF-receptor (VEGF-R) pathway. [5] Two separate phase III trials in an unselected NSCLC population demonstrated improvement in both PFS and RR with the combination of erlotinib and bevacizumab (monoclonal antibody against VEGF) compared to either agent alone, with some signal for improved activity in the EGFR mutant subgroups. [6,7] More recent literature strongly

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suggests an additive effect on PFS with the addition of bevacizumab to erlotinib in patients with EGFR mutant NSCLC (16.0 vs. 9.7 months, respectively, hazard ratio 0.54, $p = 0.0015$). [8]

Dovitinib, an oral multi-targeted receptor TKI, has a unique inhibition profile including activity against VEGFR, fibroblast growth factor receptor (FGFR), platelet derived growth factor receptor (PDGFR), and fms-related tyrosine kinase 3 (FLT-3) among other targets. This agent has demonstrated anti-tumor activity in patients with a variety of advanced solid tumors with an acceptable side effect profile, with the most common adverse events including fatigue and gastrointestinal toxicities (nausea, vomiting, anorexia, and diarrhea). [9] Compared to other VEGFR TKI agents such as sorafenib and sunitinib, dovitinib additionally targets FGFR, which contributes to growth, survival, and migration of NSCLC cells and may also be an important escape mechanism of anti-VEGFR therapy. [10] Unfortunately, despite this potential advantage, dovitinib did not provide benefit over sorafenib in the third–line setting for a different tumor type, renal cell carcinoma. [11] Furthermore, in those patients with intrinsic or acquired resistance to EGFR TKIs, FGFR may be an alternate signaling pathway contributing to NSCLC cell survival. [12–14] Indeed, the combined blockade of EFGR and FGFR was found to exert synergistic anti-proliferative effects in NSCLC preclinical models, warranting further study. [15] Thus, we conducted a phase I trial evaluating the combination of erlotinib and dovitinib for the treatment of patients with advanced NSCLC progressing after one or more prior therapies (Clinicaltrials.gov Identifier: NCT01515969). The primary objectives of the study were to characterize the safety and tolerability of the combination of erlotinib and dovitinib and to establish the maximum tolerated dose (MTD). Secondary objectives included assessment of the initial efficacy of the combination, as well as to evaluate the potential impact of dovitinib on erlotinib pharmacokinetics (PK), especially given that dovitinib is known to induce CYP1A1/1A2, which is partially responsible for erlotinib metabolism.

2. Materials and methods

2.1. Patient selection

Patients with histologically confirmed metastatic NSCLC who had failed at least 1 prior therapy, including those previously treated with erlotinib, were considered eligible for the study. The presence of an EGFR mutation was not required. Additional eligibility criteria included: $\geq$1 measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, life expectancy > 2 months, and adequate hematopoietic, hepatic, and renal function. Enrollment exclusions included patients who had received prior systemic anti-cancer therapy, radiation, or major surgery within pre-specified timeframes required for washout/recovery; history of other primary cancer within 3 years (except non-melanoma skin cancer and resected cervical carcinoma *in situ*); pregnant or breastfeeding females; active or chronic hepatitis B or C with impaired hepatic function [aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5X upper limit of normal (ULN)]; active smoking (smoking decreases serum levels of erlotinib via induction of CYP1A1/1A2) [16]; history of pulmonary embolism (PE) in last 6 months or those receiving anticoagulation treatment with therapeutic doses of warfarin or enoxaparin; interstitial pneumonitis or fibrosis; and other severe or uncontrolled medical conditions within 6 months of enrollment (i.e. left ventricular ejection fraction < 50%). The protocol was approved by our institutional review board and conducted in accordance with Good Clinical Practice guidelines. All patients provided written informed consent.

2.2. Study design and treatment plan

This was a single-site phase I standard 3 + 3 dose escalation trial of erlotinib and dovitinib in patients with EGFR wild-type or mutant metastatic NSCLC who could have previously received erlotinib. Four cohorts were planned with erlotinib dosed orally daily and dovitinib dosed orally 5 days on/2 days off, starting after a 2-week lead-in of erlotinib alone. Both erlotinib and dovitinib were taken without food, although it is now known that food does not alter the bioavailability of dovitinib. [17] The initial cohort included 3 patients (cohort 1): erlotinib 150 mg and dovitinib 300 mg. Blood samples for drug level measurements were collected on day 14 ± 4 (erlotinib alone; pre-dose, 2, 4, 6, 8, and 24 h) at erlotinib steady state (median half-life is 36.2 h). [18] Thereafter, dovitinib was added and blood samples for drug level measurements were collected on day 29 ± 4 (dovitinib + erlotinib; pre-dose, 2, 4, 6, 8, and 24 h). Patients continued on treatment until disease progression or unacceptable toxicity.

Dose escalation proceeded by standard 3 + 3 design. Dose limiting toxicity (DLT) was defined as ≥ grade 3 toxicity by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 occurring during the first 3 weeks of treatment with both drugs (after erlotinib lead-in time) with the exception of nausea, vomiting, diarrhea, or skin rash that was not optimally treated. If no DLTs occurred or 1 DLT occurred with appropriate cohort expansion from 3 to 6 patients after 3 weeks on both drugs (i.e. 5 weeks from the start of the erlotinib lead-in), dose escalation to cohort 2 would occur (erlotinib 300 mg and dovitinib 300 mg). The cohorts were built with the assumption that there may be a 20–50% reduction in the steady state concentration of erlotinib based upon CYP1A1/1A2 induction by dovitinib. [19] Therefore, cohort 2 was planned with a dose escalation of erlotinib to 300 mg based upon the results from a prior PK study with erlotinib and another CYP1A1/1A2 inducer, cigarette smoking. [16,20] Analysis of erlotinib PK from cohorts 1 and 2 was required prior to proceeding to the next cohort to ensure erlotinib levels were within therapeutic range. There was also a dose level -1 should cohort 1 not be tolerated. Only two cohorts enrolled due to DLTs [cohort 1 and (-1)] and cohort -1 was determined to surpass the MTD.

During the study, patients were monitored for safety on clinic visits day 1, 15, and 29 of cycle 1 and then once every cycle. Laboratory testing (blood chemistry, hematology) was performed weekly for the first cycle and then once per cycle. Concomitant medications were recorded throughout the study and pill count was employed to evaluate for compliance. Echocardiogram, cardiac enzymes (i.e. troponin), and an electrocardiogram (EKG) were performed at baseline. In addition, EKGs were performed on days 15 and 29 of cycle 1, and at the off-study evaluation. Tumor assessments were conducted at baseline and repeated every 8 weeks until disease progression using computed tomography imaging. Disease status was assessed by the investigator according to RECIST v1.1 criteria.

2.3. Pharmacokinetic analysis

PK parameters for erlotinib, erlotinib primary metabolite OSI-420, and dovitinib were estimated from plasma concentration data via standard noncompartmental analysis using Phoenix™ WinNonlin® (version 6.3; Certara, St. Louis, MO). The maximum concentration (Cmax) and corresponding time to maximum concentration (T_{max}) were obtained directly from the observed data. The terminal rate constant (λz) was determined by