Gastric Acid Suppression Is Associated With Decreased Erlotinib Efficacy in Non–Small-Cell Lung Cancer

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Abstract

Tyrosine kinase inhibitors (TKIs) are the focus in oncology research. As oral drugs, TKIs often have pH-dependent solubility—suggesting interactions with gastric acid suppressants (ASs). This retrospective review of 507 advanced non–small-cell lung cancer (NSCLC) patients treated with erlotinib demonstrates negative outcomes in patients concurrently receiving AS therapy; a finding also seen with sunitinib. Caution is required in this underappreciated interaction.

Background: Erlotinib is a key therapy for advanced NSCLC. Concurrent AS therapy with TKIs might reduce TKI plasma levels. Because of gastroesophageal reflux disease prevalence, this retrospective analysis was undertaken to determine if coadministering erlotinib with AS therapy affected NSCLC outcomes. **Patients and Methods:** Records of advanced NSCLC patients who received erlotinib from 2007 to 2012 at a large, centralized, cancer institution were retrospectively reviewed. Pertinent demographic data were collected and concomitant AS treatment was defined as AS prescription dates overlapping with $\geq$ 20% of erlotinib treatment duration. Records of patients who received erlotinib for $\geq$ 1 week were analyzed for progression-free survival (PFS) and overall survival (OS). **Results:** Stage IIIB/IV NSCLC patients (n = 544) were identified and 507 had adequate data for review. The median age was 64 years and 272 were female. Adenocarcinoma (n = 318; 64%) and squamous (n = 106; 21%) were predominant subtypes; 124 patients received concomitant AS therapy. In this unselected population, median PFS and OS in AS versus no AS groups were 1.4 versus 2.3 months ($P < .001$) and 12.9 versus 16.8 months ($P = .003$), respectively. Factoring sex, subtype, and performance status in multivariate Cox proportional hazards ratios for PFS and OS between AS and no AS groups were 1.83 (95% confidence interval [CI], 1.48-2.25) and 1.37 (95% CI, 1.11-1.69), respectively. **Conclusion:** This large population-based study suggests erlotinib efficacy might be linked with gastric pH and OS could be adversely affected. To our knowledge, this is the first study demonstrating a possible negative clinical effect of coadministration of erlotinib with AS therapy. Further prospective investigation is warranted.

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Introduction

Despite treatment advances, lung cancer remains the leading cause of cancer-related mortality.[1] Cytotoxic chemotherapy has been the backbone of treating advanced non–small-cell lung cancer (NSCLC). Recent strides in research have discovered the key role of the epidermal growth factor receptor (*EGFR*) pathway in driving lung cancer tumorigenesis and led to development of EGFR tyrosine kinase inhibitors (TKIs).[2]

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A commonly used EGFR TKI for advanced NSCLC is erlotinib. BR-21, a randomized phase III trial in advanced NSCLC patients who received first-line platinum-doublet chemotherapy, was the first trial to show erlotinib significantly improved progression-free survival (PFS) and overall survival (OS).[3] Predictors of EGFR TKI therapy response include Asian ethnicity, female sex, nonsmoking history, *EGFR* gene amplification, and/or presence of *EGFR*-activating mutations. In a post hoc analysis of these data, it was found that the presence of an *EGFR* mutation did not improve OS despite increased response rates.[4] BR-21 led to erlotinib adoption as a standard second- or third-line therapy in an unselected population with advanced NSCLC. Erlotinib after first-line platinum doublet chemotherapy as a "switch" maintenance approach has also been shown to improve PFS.[5] In treatment-naive, advanced NSCLC patients possessing an *EGFR*-activating mutation, erlotinib demonstrated superior response rates and PFS compared with platinum-doublet chemotherapy.[6,7]

By targeting specific cellular receptors, oral TKIs inherently have a more attractive side effect profile compared with cytotoxic chemotherapy. However, for oral medications, drug absorption can be affected by gastric acidity. During preclinical development, erlotinib was found to have pH-dependent solubility with a dissociation constant (pKa) of 5.4.[8] This pH-dependent solubility is reflected in a study that compared erlotinib plasma concentrations in healthy volunteers who were or were not taking acid suppression (AS) therapy.[9] Subjects received a 7-day course of omeprazole, a proton pump inhibitor (PPI), along with a single dose of erlotinib. There was a median decrease of 46% in the area under the concentration-time curve (AUC) in PPI-treated subjects. Similarly, a study that investigated ranitidine, a histamine type-2 receptor antagonist (H2RA), showed that ranitidine decreased erlotinib's median AUC by 33%.[8]

In addition to preclinical data, a case report documented lower than expected erlotinib trough concentrations in a patient who received intravenous pantoprazole.[10] However, lower erlotinib trough concentrations were not observed when oral pantoprazole was given. This difference was hypothesized to be because of decreased bioavailability of oral pantoprazole, resulting in decreased effects on gastric acid production compared with intravenous administration and consequently, having less effect on erlotinib absorption.

It is unclear whether decreased erlotinib absorption leads to altered clinical outcomes. Because gastroesophageal reflux disease (GERD) is highly prevalent, there is a large proportion of advanced NSCLC patients who are receiving erlotinib and AS therapy concomitantly. The objective of this retrospective cohort study was to determine AS therapy effects on clinically relevant outcomes for advanced NSCLC patients receiving erlotinib.

Patients and Methods

After institutional research ethics board approval, patients with stage IIIB or IV NSCLC who received erlotinib from 2007 to 2012 through a large, centralized single institution (catchment population of $>$ 1.8 million) were reviewed. The sixth American Joint Committee (AJCC) on Cancer staging edition was used to describe patient stage. Patients who received $\leq$ 1 week of erlotinib were excluded from this study.

Data on variables including age at diagnosis, sex, histological subtype, stage at diagnosis (using the sixth edition AJCC system), Eastern Cooperative Oncology Group (ECOG) performance status (PS), previous treatments, date of progression, and method of determining progressive disease (radiographic or clinical) were collected. Histological subtype was classified as follows: adenocarcinoma, squamous cell, large cell, poorly differentiated, or not otherwise specified (NOS).

In Alberta, Canada, a central database is used to document prescription medications. This database was interrogated to determine which patients received AS therapies. Information collected included AS therapy type (PPI, H2RA), prescription dates, method of dosing (continuous or as needed), and dose. Patients were considered to be receiving concomitant AS therapy if their AS prescription overlapped with erlotinib administration by $\geq$ 20% of the time. With a 46% decrease in AUC with 1 week of concomitant PPI use in healthy volunteers, 1 week would constitute 13% of the median PFS (erlotinib treatment duration) in the BR-21 study.[3,8] Therefore, $\geq$ 20% coadministration duration was chosen arbitrarily to include a margin of error and standardize inclusion into the AS therapy group in our study.

Clinical outcome data were collected from paper and electronic medical records. PFS and OS were analyzed in an intention-to-treat fashion using the Kaplan–Meier methods. Patients who were lost to follow-up or who stopped erlotinib early because of toxicity were included in statistical analysis. Secondary end points included objective response rate (ORR), incidence of any rash and diarrhea, incidence of dose reduction, and incidence of treatment-limiting toxicity. Statistical analysis was performed with Statistical Analysis System (SAS) version 9.3 (SAS Institute Inc, Cary, NC). All *P* values were calculated using 2-sided statistical testing and Cox proportional hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

Patients

Between January 2007 and December 2012, 544 advanced NSCLC patients received erlotinib and 507 were considered eligible for this retrospective analysis. There were 235 (46%) male patients and 272 (54%) female. The median age of the patients was 64 years (range, 28-86 years). Most patients (n = 418; 82%) had stage IV disease with the remainder having stage IIIB disease. A significant proportion of patients were PS 1 (n = 163; 32.1%) or PS 2 (n = 237; 46.7%). Although there was a greater proportion of patients with ECOG PS $\leq$ 2 in the AS group (86% vs. 79%), this did not meet statistical significance (P = .11). Most patients (n = 359; 71%) received chemotherapy before receiving erlotinib, of which platinum-doublets were most commonly used (n = 449; 88%). Histological subtypes included 64% adenocarcinoma (n = 318), 21% squamous cell (n = 106), 2% large cell (n = 11), 8% poorly differentiated (n = 43), and 6% NOS (n = 29). Eleven patients (3%) were lost to follow-up in the no AS group compared with 1 (1%) in the AS group. There was no statistically significant differences in NSCLC baseline characteristics or Charlson comorbidity index (adjusted for all patients in the study having advanced NSCLC) between the AS and no AS groups (Table 1).

Prevalence and Effect of AS

Twenty-five percent of patients (n = 124) received AS therapy and the most common therapeutic was a PPI (n = 115; 93%) with