INPLASY

Optimizing Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Treatment in Lung Cancer: The Influence of Gastric Acid Suppressants – An Updated Systematic Review and Meta-Analysis

INPLASY202450108
doi: 10.37766/inplasy2024.5.0108
Received: 22 May 2024
Published: 22 May 2024

Corresponding author:
Chi Young Kim

cykim@yuhs.ac

Author Affiliation:
Dongguk University and Yonsei University.

Kim, BK; Seong, YS; Kim, EY; Kwak, SH; Lee, SH; Lee, EH; Jang, YS.

ADMINISTRATIVE INFORMATION

Support - Dongguk University Research Fund of 2024.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202450108

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 May 2024 and was last updated on 22 May 2024.

INTRODUCTION

Review question / Objective Population
The population for our meta-analysis consists of patients undergoing cancer treatment with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs). These patients often require gastric acid suppression (GAS) therapy due to various gastrointestinal conditions, such as gastroesophageal reflux disease (GERD) or peptic ulcers. Understanding the interaction between EGFR-TKIs and GAS therapy, particularly its impact on treatment efficacy, is crucial for this population.

Intervention
The primary intervention of interest is the use of proton pump inhibitors (PPIs) as a form of GAS therapy in these patients. PPIs are widely used due to their potent acid-suppressing capabilities. However, their long-term use can significantly alter gastric pH, potentially impacting the absorption and effectiveness of EGFR-TKIs. This aspect makes PPIs a critical focus when assessing their impact on patients undergoing EGFR-TKI therapy.

Comparison
The comparison group includes patients on EGFR-TKIs who are taking GAS therapy and those who are not.

Outcomes
The primary outcomes of interest are the overall survival and progression-free survival of patients using EGFR-TKIs in conjunction with GAS therapy.

Condition being studied The condition being studied is advanced non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer, accounting for approximately 85% of all

lung cancer cases. It includes several subtypes, primarily adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The introduction of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has significantly improved the treatment landscape for patients with EGFR-mutated NSCLC, leading to better outcomes in terms of overall survival (OS) and progression-free survival (PFS). However, the concurrent use of gastric acid suppressants (GASs), such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), may interfere with the effectiveness of EGFR-TKIs, potentially compromising their therapeutic benefits.

METHODS

Participant or population The population addressed in this review consists of patients diagnosed with advanced NSCLC who are undergoing treatment with EGFR-TKIs. This group typically includes individuals with confirmed EGFR mutations, as these mutations make the cancer cells more responsive to TKI therapy. The demographic characteristics of these patients often include a higher proportion of Asian females and non-smokers, reflecting the typical clinical profile of EGFR-mutated NSCLC. This population is particularly relevant because they may also require GAS therapy for concurrent gastrointestinal conditions like GERD or peptic ulcers, making it crucial to understand the interactions between these treatments and their impact on cancer therapy outcomes.

Intervention The intervention of interest in this review is the use of gastric acid suppressants (GASs) among patients receiving EGFR-TKI therapy. GASs include proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). PPIs, such as omeprazole and esomeprazole, are commonly used due to their potent and long-lasting acid suppression effects. H2RAs, such as ranitidine and famotidine, are less potent but still effective in reducing stomach acid. The focus is on evaluating how these interventions affect the pharmacokinetics and therapeutic efficacy of EGFR-TKIs, specifically looking at outcomes like overall survival (OS) and progression-free survival (PFS).

Comparator The comparator in this review includes different patient groups to assess the impact of GASs on the efficacy of EGFR-TKIs.

Study designs to be included To address the objective of our review, we will include the following study designs: Retrospective cohort studies: These studies will provide historical data on patients who have undergone EGFR-TKI therapy and concurrently used gastric acid suppressants (GASs). They are valuable for understanding real-world outcomes and identifying long-term trends.Prospective cohort studies: These studies will follow patients over time from the initiation of EGFR-TKI therapy, allowing for direct observation of outcomes related to concurrent GAS use.Randomized controlled trials (RCTs): If available, RCT.

Eligibility criteria inclusion criteria: Studies must provide detailed data on overall survival (OS) and progression-free survival (PFS) in patients treated with EGFR-TKIs. Studies should include information on the types of GASs used (PPIs or H2RAs) and the overlap time with EGFR-TKI therapy.

Information sources The information sources for this review will include: Electronic Databases: Comprehensive searches will be conducted in PubMed, Embase, Cochrane Library, Web of Science, Scopus, and KoreaMed.
Preprint Repositories: Relevant preprints from Embase, Web of Science, and Scopus will be included to capture the most recent studies.
Supplementary Methods: References cited in included studies will be manually searched to identify additional relevant studies. This ensures a thorough and exhaustive literature search.

Main outcome(s) Overall Survival (OS): Defined as the time from the initiation of EGFR-TKI therapy to death from any cause. The effect measure will be the hazard ratio (HR) for OS, comparing patients using GASs (PPIs or H2RAs) with those not using GASs.
Progression-Free Survival (PFS): Defined as the time from the initiation of EGFR-TKI therapy to disease progression or death from any cause. The effect measure will be the HR for PFS, comparing patients using GASs with those not using GASs.

Quality assessment / Risk of bias analysis The quality assessment of primary studies will be conducted using the Newcastle-Ottawa Scale (NOS). This tool evaluates observational and cohort studies based on three broad perspectives:

Selection: Assesses the representativeness of the exposed cohort, the selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. This section can score up to 4 points.

Comparability: Evaluates the comparability of cohorts based on the design and analysis, scoring up to 2 points.
Outcome: Reviews the assessment of the outcome, the adequacy of follow-up, and the length of follow-up, scoring up to 3 points.
The total score ranges from 0 to 9 points, with studies categorized as low quality (0-3), moderate quality (4-6), and high quality (7-9).

Strategy of data synthesis Data synthesis will involve the following steps:

Data Extraction: Relevant data from each included study will be extracted using a predefined form, capturing details such as author, year of publication, study design, population characteristics, type of EGFR-TKIs and GASs used, and key outcomes (OS and PFS).
Combining Data: Hazard ratios (HRs) and their 95% confidence intervals (CIs) for OS and PFS will be pooled using a random-effects model if significant heterogeneity is detected ($I^2 > 50\%$ or p-value from the Q statistic < 0.1). Otherwise, a fixed-effect model will be used.
Heterogeneity Assessment: The I^2 statistic and Q statistic will be calculated to assess heterogeneity among studies.
Sensitivity Analysis: Sequential exclusion of each study will be conducted to determine its impact on overall heterogeneity and robustness of results.
Publication Bias: Funnel plot analysis will be used to assess publication bias.

Subgroup analysis Subgroup analyses will be performed to explore differences in outcomes based on:

Type of GASs: Comparing the impact of PPIs versus H2RAs on OS and PFS.
Duration of GAS Overlap: Assessing how different durations of overlap between GAS and EGFR-TKI use affect OS and PFS.

Sensitivity analysis Sensitivity analyses were conducted by sequentially excluding each study.

Language restriction The review will include studies published in English. This language restriction is applied to ensure a consistent level of detail and quality in the studies analyzed and to facilitate accurate.

Country(ies) involved S.Korea.

Keywords lung neoplasm, tyrosine kinase inhibitors, proton pump inhibitors; histamine H2 antagonists; survival analysis, drug interactions.

Contributions of each author
Author 1 - Beong Ki Kim.
Author 2 - Ye Seul Seong.
Author 3 - Eunyoung Kim.
Author 4 - Sehyun Kwak.
Author 5 - Sanghoon Lee.
Author 6 - Eunhye Lee.
Author 7 - Yoonsoo Jang.
Author 8 - Chi Young Kim.