OncoTargets and Therapy

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ORIGINAL RESEARCH

Combination Use of First-Line Afatinib and Proton-Pump Inhibitors Reduces Overall Survival Among Patients with EGFFR Mutant Lung Cancer

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Purpose: Previous retrospective studies reported that proton-pump inhibitors (PPIs) may decrease the efficacy of first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) including gefitinib and erlotinib. Afatinib had a wider soluble pH range, with possible fewer interactions with antacids. However, clinical data were limited. Thus, this study aimed to evaluate the negative impact of PPIs on afatinib.

Patients and Methods: This retrospective cohort study included patients who are newly diagnosed with non-small cell lung cancer (NSCLC) from 2014 to 2019 using the Chang Gung Research Database. We identified patients who were treated with first-line afatinib and analyzed the association between the PPI and afatinib treatment outcomes.

Results: A total of 1418 patients were treated with first-line afatinib and followed up for 6 years. First-line afatinib was administered to 918 eligible patients, and 330 had afatinib with PPIs. The combination use of PPIs and afatinib significantly decreased the overall survival (OS) compared with that of patients using afatinib only (median OS: 33.2 and 25.1 months, $p < 0.01$) and multivariate analyses (Combination use: hazard ratio: 1.29; 1.05–1.59, $p = 0.01$). The percentages of patients who were able to receive 2nd line therapy also significantly decreased in afatinib with PPI cohort.

Conclusion: The concurrent use of PPIs was associated with lower OS in patients with EGFR-mutant lung cancer under the first-line afatinib treatment but not associated with TTF.

Keywords: proton-pump inhibitor, epidermal growth factor receptor tyrosine kinase inhibitor, non-small cell lung cancer, afatinib, Chang Gung Research Database

Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the standard of care for patients with EGFR-mutant lung cancer,[1] with good clinical response and extended progression-free survival (PFS), and even overall survival (OS) than traditional chemotherapy. The second-generation EGFR-TKIs, including afatinib and dacomitinib, are irreversible inhibitors, which covalently bind to pan-ErbB receptors and demonstrate more potent efficacy in EGFR inhibition than first-generation EGFR TKIs.[2] In past years, researchers evaluate the impact of proton-pump inhibitors (PPIs) on EGFR-TKIs because first-generation EGFR-TKIs, such as gefitinib or erlotinib, were both pH-dependent solubility by oral administration.[3]

Pharmacokinetic data showed the area under the plasma concentration curve (AUC) of gefitinib, which was reduced by 44%, and the maximum observed plasma concentration (C_{max}) by 70% after taking ranitidine, which is a histamine 2 receptor antagonist (H_2RA). Erlotinib and dacomitinib also had significantly reduced AUC and C_{max},[4] but afatinib was not altered by this interaction.[5] Afatinib had a highly soluble pH range (1–7.5) and may therefore have fewer antacid interactions.[6]

Received: 22 August 2022
Accepted: 21 December 2022
Published: 28 December 2022

Previous retrospective or cohort studies reported the negative impact of PPIs on first-generation EGFR-TKIs,[7–19] and several systemic review and meta-analysis report similar results.[20–22] However, clinical data to evaluate the negative impact of PPIs on second-generation TKIs, such as afatinib or dacomitinib, are limited. Therefore, this retrospective cohort study was designed using Chang Gung Research Database (CGRD) to evaluate the impact of PPIs on first-line afatinib treatment outcomes.

Materials and Methods

Data Source

The Chang Gung Medical Foundation (CGMF) is a medical and hospital network consisting of seven branches of Chang Gung Memorial Hospitals (CGMHs) and is the largest medical system in Taiwan. CGMF has 10,070 beds, with >280,000 patient admissions each year. All seven branches use electronic medical records for medical practice. The CGRD is a deidentified database comprised multi-institutional standardized electronic medical records since 2000.

Inclusion Criteria

We identified lung cancer patients more than 18 years old receiving first-line afatinib according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) code C34.0-C34.9 from 2014 to 2019 using the CGRD.

Exclusion Criteria

Patients with double cancers, including other non-lung cancers or combined with small cell carcinoma, were excluded. Patients should have EGFR L858R or Exon 19 deletion, and other uncommon or compound mutations were excluded. We identified patients who received prior line chemotherapy using ATC codes including cisplatin, carboplatin, pemetrexed, vinorelbine, paclitaxel, docetaxel, and gemcitabine, to exclude patients who were not taking first-line afatinib. Afatinib used for less than 90 days or multiple EGFR-TKIs at the same time were also excluded in this analysis. Patients who change to other EGFR-TKIs after stopping afatinib within 28 days were excluded from analyses because these groups of patients usually change TKIs because of adverse effects of afatinib rather than disease progression.

Definition of First-Line Afatinib

Afatinib was approved and reimbursed by Taiwan National Health Insurance (NHI) in 2014. All patients were ascertained by the Cancer Registry Database from CGRD, which is a subset of the Taiwan's nationwide cancer registry, and pathological confirmation of lung cancer is required to apply for this certification.[23,24] The Anatomical Therapeutic Chemical (ATC) code was used to identify patients with NSCLC who received afatinib or other anticancer agents. According to the NHI policy, physicians must seek approval every 3 months when prescribing first-line afatinib with initial pathological diagnosis, EGFR mutation type analysis, and image evidence confirming advanced lung cancer in patients.

Moreover, the NHI policy recommends physicians to reapply afatinib every 3 months according to the tumor response as evaluated by image studies with chest computed tomography, bone scans, and brain magnetic resonance imaging, which must be peer-reviewed. NHI policy states that afatinib use is not allowed beyond radiological progression. Thus, patients taking first-line afatinib without previous chemotherapy must have late-stage EGFR-mutant primary lung cancer. Those treated with first-line afatinib were followed from the index date of afatinib use until treatment failure, death, or the end of 2019. Time to treatment failure (TTF) was defined as the time from the start of the first-line treatment to the last day of receiving afatinib. The last prescription date was further confirmed by observing no additional prescription of afatinib within the subsequent 28 days.

Definition of PPIs

Using ATC codes, including A02BC01 (omeprazole), A02BC03 (lansoprazole), A02BC05 (esomeprazole), A02BC02 (pantoprazole), A02BC04 (rabeprazole) andA02BC06 (dexlansoprazole), we identified patients who were prescribed PPIs after starting the EGFR-TKI therapy.

Covariates

We retrieved data for patients' baseline characteristics, including age and gender. Comorbidities, including hypertension, diabetes mellitus, coronary artery disease, ischemic stroke, chronic obstructive pulmonary disease, peptic ulcer, and chronic kidney disease, were defined from ICD-9/ICD-10 in OPD or IPD diagnosis from January 1, 2014, to December 3, 2019.

Statistical Data Analysis

Differences between combination drugs and not were evaluated using the chi-square test and Student's *t*-test for categorical and continuous variables, respectively. The TTF and OS curves were calculated using the Kaplan–Meier method and compared between-group differences using the Log rank test. The association of TTF, OS, and combination drugs and not were evaluated with Cox proportional hazards regression models to compute hazard ratios (HRs) with 95% confidence intervals (CIs) after adjusted for potential risk factors. Variables, including age, gender, performance status, clinical cancer staging, smoking, and comorbidities, were included in the multivariable analysis. Statistical significance was defined as *p*-values of <0.05. All analyses were performed using the SAS version 9.4 (SAS Inc., Cary, NC, USA).

Ethical Standards

Ethics approval was obtained from the Institutional Review Board of CGMH (approval number: CGMHIRB No.202001040B0) and conformed to the Helsinki Declaration. Informed consent was waived because all data were anonymized from existing databases and results were presented in aggregates.

Results

We identified a total of 1418 patients newly diagnosed with lung cancer from CGRD, aged 18 years or older, receiving afatinib from 2014 to 2019 (Figure 1). We excluded 500 patients, among them 29 were double cancers, including 26 other than lung cancer and 3 combined with small cell lung cancer; 106 received chemotherapy before EGFR-TKIs treatment; 323 received afatinib treatment of <90 days; and 108 received other EGFR-TKIs. Finally, 918 patients were

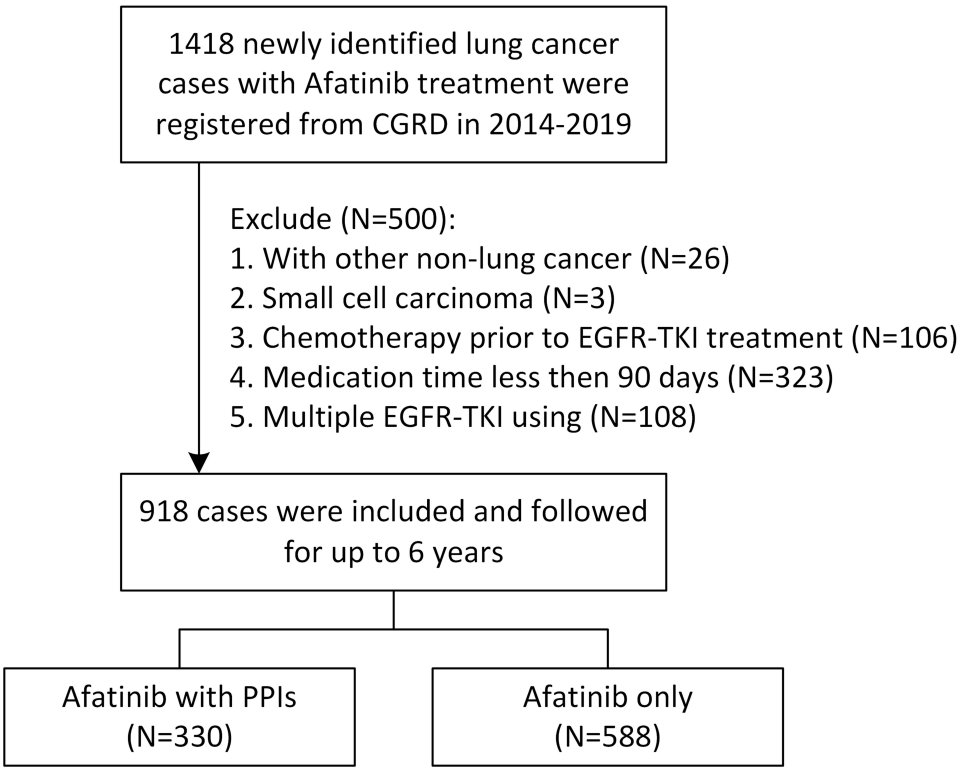

Figure 1 Flowchart of study design.

Table 1 Baseline Characteristics

Variable	Afatinib with PPIs	Afatinib Only	P-value
	N (%)	N (%)	
Total	330	588	
Gender			0.643
Male	134 (40.6)	248 (42.2)	
Female	196 (59.4)	340 (57.8)	
Age (years)			0.680
Young (≤ 65)	189 (57.3)	345 (58.7)	
Old (> 65)	141 (42.7)	243 (41.3)	
Mean (SD)	63.3 (11.2)	63.0 (11.0)	0.672
Smoking status			0.137
Ever	49 (14.8)	72 (12.2)	
Never	279 (84.6)	504 (85.7)	
Missing	2 (0.6)	12 (2.0)	
Comorbidities			
Hypertension	122 (37.0)	197 (33.5)	0.290
Diabetes mellitus	54 (16.4)	70 (11.9)	0.058
Coronary artery disease	31 (9.4)	31 (5.3)	0.017*
Stroke	12 (3.6)	23 (3.9)	0.835
COPD	51 (15.5)	81 (13.8)	0.487
Peptic ulcer	124 (37.6)	99 (16.8)	<0.001*
Chronic kidney disease	13 (3.9)	17 (2.9)	0.391
Charlson index (mean, SD)	7.2 (3.2)	6.5 (3.4)	0.001*

Note: *p value < 0.05.
Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

included in our study cohort and followed up for 6 years. Among 918 patients, 330 were concurrently using EGFR-TKIs and PPIs, defined as afatinib with PPI cohort, and 588 were afatinib-only cohort. Among afatinib with PPI cohort, patients received 152.7 days of PPIs in average and standard difference was 258.3 days.

Table 1 shows the baseline characteristics of the two cohorts. The mean age in the afatinib with PPI cohort was 63.3 (±11.2) years, and 59.4% of the patients were female; whereas, the mean age in the afatinib-only cohort was 63.3 (±11.2) years old and 57.8% were females. Both cohorts were mostly never smokers (84.6% vs 85.7%). Comorbidities among both cohorts, including hypertension (37.0% vs 33.5), diabetes mellitus (16.4% vs 11.9%), stroke (3.6% vs 3.9%), chronic obstructive pulmonary disease (15.5% vs 13.8%), and chronic kidney disease (3.9% vs 2.9%). The afatinib with PPI cohort had more coronary artery disease (9.4% vs 5.3%), significantly peptic ulcer (37.6% vs 16.8%), and also higher Charlson index (7.2 ± 3.2 vs 6.5 ± 3.4).

The median TTF in the afatinib with PPI cohort was 15.3 months (95% CI: 15.1–17.7 months) after 6 years using the Kaplan–Meier method, without significant differences from the afatinib-only cohort (median TTF: 16.5, 95% CI: 14.3–17.0 months) (Figure 2). The median OS in the afatinib with PPI cohort was 25.1 months (95% CI: 22.6–29.9 months), which is significantly lower than the afatinib-only cohort (median OS: 25.1, 95% CI: 22.6–29.9 months, log-rank p = 0.006) (Figure 3).

Multivariate analyses, with the afatinib-only cohort as the reference, revealed a crude hazard ratio (HR) of TTF as 1.09 (95% CI: 0.92–1.29) and adjusted HR as 1.08 (95% CI, 0.91–1.29), without statistical significance. Multivariate analyses of OS demonstrate that compared to afatinib only, the concurrent use of afatinib with PPIs had a higher risk of mortality. Crude HR was 1.32 (95% CI: 1.09–1.61) and adjusted HR was 1.29 (1.05–1.59). PPIs are an independent risk factor for decreased OS (Table 2). After 1st line afatinib for EGFR mutant lung cancer, most patients accepted chemotherapy. There was no significance of 2nd line treatment choices between with or without PPI cohorts, and similar

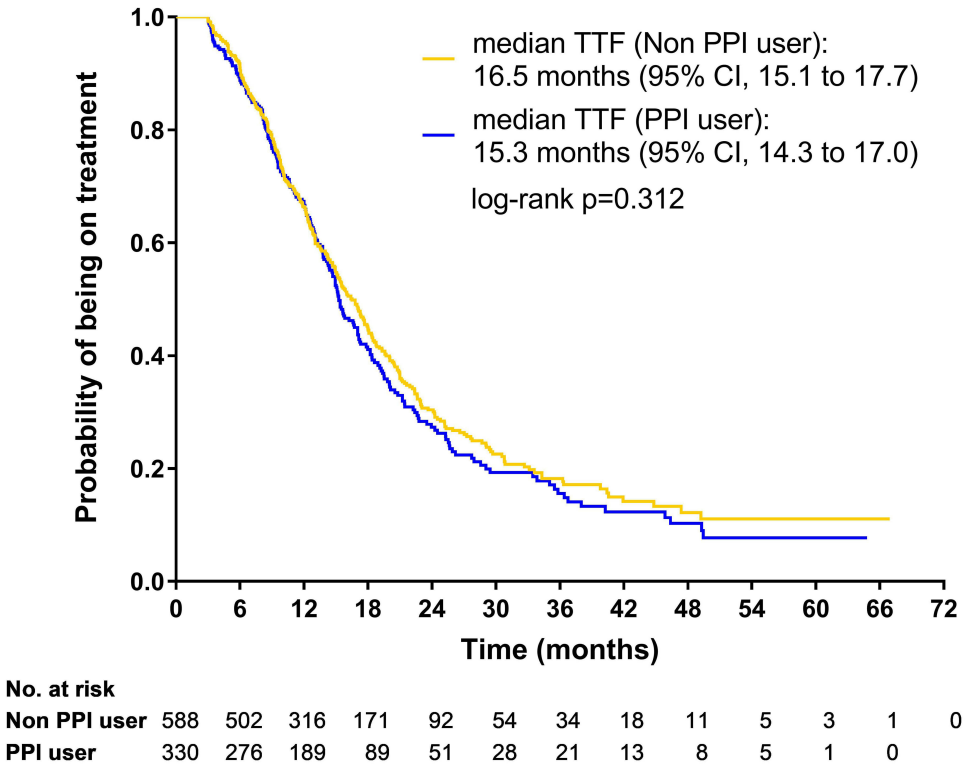

Figure 2 Kaplan–Meier analysis of probability of being on treatment for patients using PPI and not.

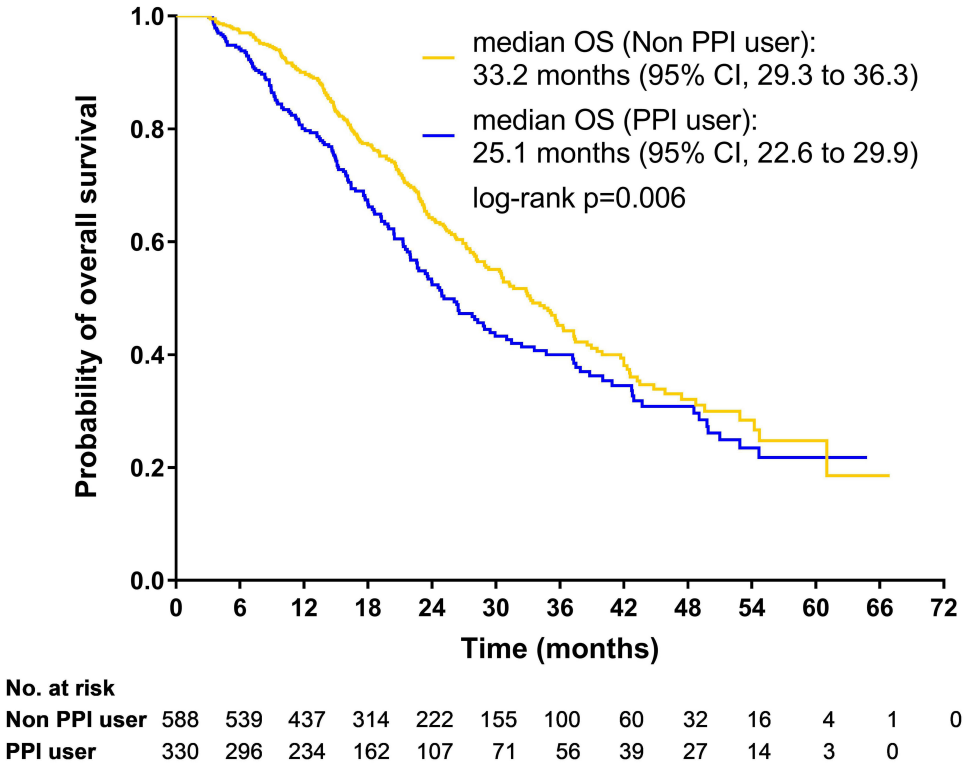

Figure 3 Kaplan–Meier analysis of probability of overall survival for patients using PPI and not.

Table 2 Multivariate Cox Regression Analysis of TTF and OS for Patients Using Afatinib with PPI and without PPI

Outcomes	Median Survival Time (Months, 95% CI)		Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
	Non PPI User	PPI User				
TTF	16.5 (15.1–17.7)	15.3 (14.3–17.0)	1.09 (0.92–1.29)	0.312	1.08 (0.91–1.29)	0.396
OS	33.2 (29.3–36.3)	25.1 (22.6–29.9)	1.32 (1.09–1.61)	0.006	1.29 (1.05–1.59)	0.014*

Notes: Cox model adjusted for sex, age group, smoking status, comorbidities, and Charlson index. *p value < 0.05.
Abbreviations: HR, hazard ratio; TTF, time to treatment failure; OS, overall survival.

Table 3 Second-Line Therapy and Later-Line Osimertinib Using Status After Failure Treatment with First-Line Afatinib

Variable	Afatinib with PPIs	Afatinib Only	P-value
	N (%)	N (%)	
Total	222	362	
With later-line treatment			0.001
No	115 (51.8)	138 (38.1)	
Yes	107 (48.2)	224 (61.9)	
Second-line therapy			0.706
Osimertinib	11 (10.3)	17 (7.6)	
Gefitinib/Erlotinib	5 (4.7)	10 (4.5)	
Chemotherapy	91 (85.0)	197 (87.9)	
Later-line Osimertinib using			0.952
No	207 (93.2)	338 (93.4)	
Yes	15 (6.8)	24 (6.6)	

proportions of patients received later-line osimertinib using. However, afatinib with PPIs cohort had significant lower percentages of patients able to receive 2nd line therapy (48.2% vs 61.9%, p = 0.001) (Table 3).

Discussion

This CGRD cohort study demonstrates that concurrently received PPIs among patients with first-line afatinib for EGFR-mutant lung cancer independently increases the mortality of patients but not reducing the TTF. Afatinib with PPI cohorts had significant lower percentage of patients able to receive 2nd line therapy. The combination use of PPIs and afatinib should be cautious.

The United States Food and Drug Administration recommended avoiding the combination use of EGFR-TKIs with PPIs. In this present study, we found that 35.94% of patients with lung cancer taking first-line afatinib concurrently received PPIs. The Taiwan NHI database revealed a 24.17% combination use of PPIs with gefitinib.[14] Afatinib had a relatively higher dissolution rate throughout the physiologic pH range (1–7.5) than gefitinib or erlotinib.[5] In theory, traditionally afatinib may have fewer interactions with antacid agents. Physicians may prescribe more afatinib than gefitinib or erlotinib when patients have to use PPIs, resulting in a higher percentage of patients using afatinib with PPIs than gefitinib or erlotinib. A Dutch Multidisciplinary Expert group is assessing the clinical significance of PPIs in oncology and provides recommendations for PPI management. EGFR-TKIs, including dacomitinib, erlotinib, and gefitinib, have been recommended to separate the dose from PPIs or H2-receptor antagonists. However, afatinib had no similar recommendations about drug interactions with antacids.[25]

Previous retrospective or cohort studies reported the impact of PPIs on first-generation EGFR-TKIs (Table 4). Several systemic reviews and meta-analyses also demonstrated that antacids are significantly associated with increased mortality

Table 4 Studies of the Impact of Antacid Agents on EGFR-TKIs in Patients with Lung Cancer

	Author	Line of TKIs	EGFR-TKIs Only Group		Combination Use Group		Antacid Rate	PFS* HR (95% CI)	OS HR (95% CI)
			EGFR TKIs	N	Antacid	N			
2013	Hilton et al[7]	2nd line	Erlotinib	295	PPIs, H_2RA	190	39.18%	1.75(1.43–2.13)	1.67 (1.34–2.05)
2015	Chu et al[8]	All	Erlotinib	383	PPIs, H_2RA	124	24.46%	1.83 (1.48–2.25)	1.37 (1.11–1.69)
2016	Kumarakulasinghe et al[9]	NA	Gefitinib, Erlotinib	102	PPIs, H_2RA	55	35.03%	1.37 (0.89–2.12)	1.47 (0.92–2.35)
2016	Zenke et al[10]	All	Gefitinib, Erlotinib	83	PPIs, H_2RA	47	36.15%	1.15 (0.73–1.79)	1.41 (0.83–2.35)
2016	Chen et al[19]	1st line	Gefitinib, Erlotinib	212	PPIs, H_2RA	57	21.19%	NA	2.27 (1.26–4.11)[b]
2016	Lam et al[11]	All[a]	Erlotinib	52	PPIs, H_2RA	24	31.58%	NA	NA
2018	Sedano et al[12]	All	Gefitinib, Erlotinib	45	PPIs, H_2RA	118	72.39%	2.50 (1.61–3.88)	NA
2019	Sharma et al[13]	All	Erlotinib	NA	PPIs	NA	22.70%	1.09 (0.92–1.10)	1.11 (1.02–1.20)
2019	Fang et al[14]	1st line	Gefitinib	969	PPIs	309	24.18%	1.11 (0.91–1.36)[c]	1.67 (1.33–2.09)[c]
2020	Saito et al[15]	All	Gefitinib	56	H_2RA	31	35.63%	0.95 (0.60–1.48)	0.86 (0.52–1.43)
2020	Su et al[16]	1st line	Gefitinib, Erlotinib, afatinib	761	PPIs, H_2RA	92	10.79%	0.89 (0.69–1.15)	1.01 (0.75–1.36)
2021	Li et al[17]	1st line	Gefitinib	159	PPIs	70	30.57%	1.08 (0.61–1.94)	1.01 (0.56–1.82)[d]
	Li et al[17]	1st line	Dacomitinib	152	PPIs	83	35.32%	1.35 (0.69–2.65)	1.19 (0.65–2.18)[d]
2022	Lee et al[18]	1st line	Gefitinib	2842	PPIs, H_2RA	1498	34.52%	1.37 (1.24–1.52)[b]	1.58 (1.42–1.76)[b]
	Lee et al[18]	1st line	Erlotinib	719	PPIs, H_2RA	916	56.02%	1.19 (1.01–1.39)[b]	1.54 (1.30–1.82)[b]
2022	**Ho et al (This study)**	1st line	**Afatinib**	588	PPIs	330	35.95%	1.08 (0.91–1.29)	1.29 (1.05–1.59)

Notes: [a]All cancers (not lung cancer only); [b]Combination use with PPIs group; [c]High coverage ratio group; [d]Extensive PPIs users; *PFS or TTF or TTNT according to study design.
Abbreviations: PFS, progression free survival, TTF, time to treatment failure, TTNT, time to next therapy; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; PPIs; NA: not available.

risk in patients with lung cancer receiving EGFR-TKIs.[20–22] However, data of afatinib and PPIs remained limited. Second-generation EGFR-TKIs, such as afatinib and dacomitinib, showed a better survival benefit than first-generation EGFR-TKIs, such as gefitinib and erlotinib.[26,27] Third-generation EGFR-TKIs, such as osimertinib, showed good survival outcomes in the FLAURA trial, first-line osimertinib is now considered as the preferred option in first line for patients with a tumor with sensitizing EGFR mutations and efficacy is highly demonstrated also in Asiatic patients.[28,29] Taiwan NHI reimburses osimertinib only in lung cancer with exon 19 deletion combine brain metastases. Thus, afatinib is still often used in a real-world setting in Taiwan.

Afatinib is highly soluble throughout the physiologic pH range (1–7.5) and may, therefore, have fewer interactions with acid-reducing drugs.[6] A retrospective analysis using data from a randomized controlled trial ARCHER 1050 revealed no significant difference in plasma concentrations of dacomitinib for each dose level between the reference versus PPI users or the reference versus extensive PPI users.[17] PFS and OS were significantly lower in PPI users and extensive PPI users in univariable analyses but with no significance after incorporating all specified potential confounders. However, a 39% decreased dacomitinib AUC was found in a dedicated healthy volunteer study.[30] No plasma concentration difference was found after using PPIs in a well-designed Phase III randomized controlled trial may be because physicians well understood the possible drug–drug interaction and patients were well educated to separate the timing of taking PPIs and TKIs, which do not reflect the real-world condition. Other retrospective analyses from single-center data revealed no significant difference in OS and TTF between antacid users and nonusers.[16] However, only 10.79% of the patients received PPIs or H_2RA, which was much lower than other Taiwan NHI database studies (PPIs: 24.18%, PPIs or H_2RA: 34.52%, 56.02%, respectively).[14,18] Single-center retrospective study unable to access patients who get drugs from other hospitals, local clinics, and pharmacies over the counter may underestimate the proportion of patients using antacids. A recent study to evaluate the effects of CYP3A4 variants on the metabolism of osimertinib showed plasma concentrations of osimertinib decreased significantly after co-administration with rabeprazole orally. The disposition of osimertinib could be remarkably influenced by genetic polymorphism and proton pump inhibitors.[31] Oxidative CYP-mediated metabolism of afatinib had much lower importance because of the minimal biotransformation.

Drug–drug interactions arising from inhibition or induction of CYP450 enzymes by concomitant medications are unlikely to occur.[5]

PPIs may not only reduce the clinical efficacy of EGFR-TKIs via a reduced plasma concentration of TKIs. Additionally, a meta-analysis showed negative association in patients with advanced lung cancer who received chemotherapy and PPIs in subgroup analyses.[21] Several retrospective reports also showed worse outcomes in patients with lung cancer who received combination use of PPIs and ICIs.[32] However, the influence of PPIs on ICIs remained controversial.[33–35] In this present study, we found that afatinib with PPI cohort had significant lower percentage of patients able to receive 2nd line therapy, which means patients stop treatment rather than lung cancer on progression only but general condition downhill caused 2nd line chemotherapy unavailable. Patients with lung cancer were at high risk of developing pneumonia than patients with other cancer types. Therefore, the use of PPI was assumed to place patients with lung cancer to be more susceptible to infection. Besides, PPIs influence the gut microbiota.[36] The crosstalk between the gut microbiota and the immune system contributes to the health status of the host. Patients with melanoma who respond to nivolumab treatment had less abundance of *Ruminococcus bromii*, *Dialister*, and *Sutterella* spp. than not responders.[37] Long-term PPI users had significantly higher amounts of *Ruminococcus* in patients with gastroesophageal reflux disease.[38] Thus, PPIs can lead to bacterial dysregulation, thereby reducing the clinical efficacy of immunotherapy, but further research is needed to confirm the theory.

Strengths and Limitations

The strengths of this study include the large real-world cohort to evaluate the possible effects of PPIs on afatinib by adopting the active comparator controls. Moreover, the present study included important data, such as EGFR mutation and self-paid drugs, which were unavailable in the Taiwan NHIRD. However, we acknowledged some limitations. First, assessing the actual medication adherence in retrospective settings is difficult, which may cause possible bias. Second, PPIs and antacids may be from local clinics or pharmacies over the counter; thus, we may underestimate the proportion of patients using PPIs. Third, we did not obtain medical records from outside the CGRD in Taiwan, which may have led to a loss of follow-up. Fourth, the CGRD population may differ from those of the national database (NHIRD) and usually under more severe conditions.[39] Fifth, we analyzed the effect of PPIs on afatinib treatment, but data were unavailable for osimertinib or dacomitinib from the CGRD, and only 20 patients use first-line osimertinib or dacomitinib in our study period; thus, we only focused on afatinib. Sixth, afatinib had more adverse effects including skin rash and diarrhea compared with 1st-generation EGFR-TKIs.[40] However, in this database cohort study using CGRD, adverse effects of drugs were not well recorded and structured. We were unable to evaluate if PPIs increase the adverse effects of EGFR-TKIs. Finally, we could not conclude that PPIs directly decrease the OS of patients receiving afatinib, but a combination use of PPIs and afatinib was associated with reduced OS through an unknown mechanism. To our knowledge, this is the first and the largest nationwide cohort study to access the impact of PPI use on patients with EGFR-mutant lung cancer who received first-line afatinib.

Conclusion

The concurrent use of PPIs significantly negatively impacts on overall survival in patients with advanced lung cancer who received first-line afatinib. Physicians should be cautious in concurrently prescribing afatinib and PPIs.

Abbreviations

ATC, Anatomical Therapeutic Chemical; CGMF, Chang Gung Medical Foundation; CGRD, Chang Gung Research Database; CI, Confidence intervals; FDA, Food and Drug Administration; HR, Hazard ratio; ICI, Immune checkpoint inhibitors; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NSCLC, Non-small cell lung cancer; OS, Overall survival; PPI, Pump inhibitors; TTF, Time to treatment failure.

Availability of Data and Materials

No additional data is available.

Ethical Approval and Informed Consent

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 200.

Acknowledgments

We would like to thank the Health Information and Epidemiology Laboratory of Chang Gung Memorial Hospital, Chiayi Branch, for the comments on and assistance with data analysis. The authors would like to thank Enago for providing professional English edited services.

Funding

This study was supported by a grant from Chang Gung Memorial Hospital, Chia-Yi branch, Taiwan (CGRPG6K0041). This funding body played no role in the study design, analysis, and interpretation of data in this paper.

Disclosure

The authors have no conflicts of interest relevant to this article.

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