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ORIGINAL ARTICLE

Clinical impact of gastric acid suppressing medication on the effectiveness of tyrosine kinase inhibitors in lung cancer patients

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Summary

Purpose: *Erlotinib and gefitinib are both tyrosine kinase inhibitors (TKIs) approved for the treatment of non-small cell lung cancer (NSCLC). Although it is well known that the increase of gastric pH may decrease the solubility of TKIs, there is limited evidence about the clinical repercussion of this fact. The purpose of this study was to determine if the use of gastric acid suppressive therapy (As) concomitantly with TKIs has an adverse impact on progression-free survival (PFS) and to determine whether the type of drug used (proton pump inhibitors/PPIs or histamine-2 receptors antagonists (H2RAs) may influence it.*

Methods: *In this retrospective observational study included were patients treated for ≥1 week with erlotinib or gefitinib from January 2012 to December 2015. Demographic, diagnostic and therapeutic variables were collected. Patients were divided into two groups (As users and non-As users). For the calculation of the PFS the Kaplan Meier and multivariate Cox regression analysis were used.*

Results: *163 patients with mean age 70 years were included. 72.39% (n=118) received TKIs and As concomitantly. The mean PFS was 84 days (95% CI, 65-101) and 221 days (95% CI, 125-429; p <0.0001) in As users and non-As users, respectively. Regarding the type of As used, no significant differences were observed.*

Conclusion: *Concomitant use of As and TKIs adversely impacted the PFS outcomes in NSCLC patients regardless of the type of As used. Further studies are needed to determine the clinical impact of interactions between antiacids and antineoplastics.*

Key words: *erlotinib, histamine-2 receptor antagonist, gefitinib, progression free survival, proton pump inhibitor*

Introduction

Despite advances in cancer therapy, lung cancer is today the leading cause of cancer related deaths globally. The mean age at the onset of lung cancer ranges from 55 to 75 years, being more frequent in men than in women [1]. NSCLC accounts for approximately 85% of all lung cancer subtypes [2]. For years, the main way to treat NSCLC in advanced stages has been conventional chemotherapy. However, advances in research have revealed the key role of the epidermal growth factor receptor (EGFR) in this type of cancer. This discovery led to the development of EGFR TKIs [3]. Erlotinib and gefitinib are the most commonly used TKIs for NSCLC.

Multiple randomized clinical trials have shown that erlotinib and gefitinib, used as first-line

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treatment, have a clinical benefit in EGFR-positive NSCLC patients, achieving response rates of 62% to 83% and a median PFS of 9.2 to 13.1 months versus standard double platinum-based chemotherapy [4–8]. The BR-21 trial allowed erlotinib to be positioned as second- or third-line therapy for any type of NSCLC after a first-line double-platinum-based treatment, demonstrating an improvement in PFS [9].

In the last years, targeted therapies have gained prominence not only because of their potential to improve survival, but for their adverse effects profile, superior to that of conventional chemotherapy [4–8].

Erlotinib and gefitinib have chemical properties of a weak base, with a pH-dependent solubility [10–12]. The acid dissociation constant (pKa1) is similar (pKa=5.4) for both drugs [10]. This causes that under hypochlorhydric conditions induced by acid suppression therapy (As), the intragastric pH rises from ~1.2 to ~4, and the equilibrium changes from the ionized to the non-ionized form, which is more difficult to absorb. This pH-dependent drug-drug interaction may therefore decrease drug absorption and exposure in the body and, consequently, the clinical efficacy of erlotinib and gefitinib.

Gastric acid-suppressing medications are widely used by the general population, and many lung cancer patients use them for gastroesophageal reflux disease. A US study found that the prevalence of antacid use was 33.2 - 46.3% among patients with lung cancer [10].

Erlotinib area under the concentration-time curve (AUC) and maximum plasma concentration (Cmax) was reduced by 46 and 61% respectively in subjects who took a PPI (omeprazole) versus those who only received erlotinib [11]. In a similar study with an H2RAs (ranitidine), AUC and Cmax decreased by 33 and 54% respectively in the group that received the H2RAs together with erlotinib versus those who only received the TKI [13]. Regarding gefitinib, in another study using ranitidine at high doses, gefitinib AUC and Cmax were reduced by 44 and 70%, respectively [14].

Although it is well known that the increase of gastric pH may decrease the solubility of TKIs, there is limited evidence about the clinical repercussion of this fact.

Methods

Study patients and data collection

In this retrospective observational study all patients who started treatment with erlotinib or gefitinib in a third-level hospital between January 2012 and December 2015 and had been on treatment ≥1 week were included.

Data collection included the following:

a. Demographics: age and sex at the beginning of treatment.
b. Diagnosis: stage of disease, histological subtype, existence of brain metastases, functional status at the beginning of treatment and presence of EGFR mutation.
c. Therapeutics: type of TKI used, treatment line and previous treatments, best response achieved during treatment with TKI, date and reason for treatment discontinuation and type of antacid used.

The stage of the disease was classified according to the sixth edition of the AJCC (American Joint Committee on Cancer) system. Lung carcinoma was classified according to different histological subtypes: adenocarcinoma, squamous, undifferentiated, large cells, adenosquamous or unspecified. Patient's functional status at the beginning of treatment was classified according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale. Progression of the disease was assessed clinically or radiologically.

For patient identification and data collection, the outpatient hospital pharmacy drug dispensing software, hospital and primary care electronic medial records and oncology prescribing order entry software were used.

Patients were divided into two groups: a) As users: patients who took any type of As concomitantly with a TKI and b) non-As users: patients who were taking a TKI, without any As.

Patients were classified as As-users if the periods of As and TKI therapy overlapped by ≥20%. Subsequently, As-users were divided into two subgroups: PPI users and H2RA users.

Statistics

Two survival analyses were performed. PFS was defined as the time from the beginning of treatment to progression of disease or death. Survival analysis was performed using Kaplan Meier method. In the first analysis, As-users were compared to non-As users. In the second analysis, PPI-users were compared to H2RA-users. The differences between both groups were determined using the log rank test. Patients who continued treatment at the end of the study and those who discontinued TKI for a reason other than disease progression were included in the statistical analysis. Baseline differences in clinical and demographic characteristics were assessed using the x^2 test or the Fisher exact test, as appropriate.

All p values were calculated using 95% confidence interval (CI), and statistical significance was considered with $p<0.05$. In addition, a multivariate analysis was performed using Cox regression model to identify the independent variables associated with disease progression.

Statistical analysis was performed using "Analysis con R" software version 3.1.2 (2014-10-31) and survival package R Core Team (2014).

Results

Patients

195 NSCLC patients were included, and 163 of them had complete data for further analysis. The median age of the patients was 70 years (range 39-89) and 64.42% (n=105) were men. Most patients (n=145, 88.96%) had stage IV disease at baseline, and the rest had stages IIIA or IIIB. The main histological subtype was adenocarcinoma (n=97, 59.51%), followed by squamous cell (n=53, 32.52%), large cell (n=5, 3.07%), undifferentiated (n=2, 1.23%) and adenosquamous carcinoma (n=1, 0.61%). 82.21% (n=134) of the patients did not present brain metastases and 67.48% (n=110) had ECOG PS 0-1 at the beginning of treatment with TKI. EGFR mutation was positive in 25.77% (n=42) of the patients, negative in 39.26% (n=64) and unknown in 34.97% (n=57).

Regarding the therapeutic variables, 84.05% of the patients (n=137) were treated with erlotinib and 15.95% (n=26) with gefitinib. 77.3% (n=126) of the patients received chemotherapy before starting

Table 1. Demographic, diagnostic and therapeutic variables of NSCLC patients depending on whether or not they received As concomitantly with a TKI (n=163)

Characteristics	*Total (n=163) n (%)*	*Non-As users (n=45) n (%)*	*As users (n=118) n (%)*	*p value*
Mean age years, mean±SD	69.73	67.13 (±10.84)	70.61 (±10.97)	0.072
Sex				0.851
Men	105 (64.42)	30 (66.67)	75 (63.56)	
Women	58 (35.58)	15 (33.33)	43 (36.44)	
TNM				0.999
IIIA	8 (4.91)	2 (4.44)	6 (5.08)	
IIIB	10 (6.13)	3 (6.67)	7 (5.93)	
IV	145 (88.96)	40 (88.89)	105 (88.98)	
Histology				0.590
Adenocarcinoma	97 (59.51)	30 (66.67)	67 (56.78)	
Squamous cell	53 (32.52)	13 (28.89)	40 (33.90)	
Large cell	5 (3.07)	-	5 (4.24)	
Not-specified	5 (3.07)	1 (2.22)	4 (3.39)	
Undifferentiated	2 (1.23)	1 (2.22)	1 (0.85)	
Adenosquamous	1 (0.61)	-	1 (0.85)	
Brain metastases				0.251
Yes	29 (17.79)	5 (11.11)	24 (20.34)	
No	134 (82.21)	40 (88.89)	94 (79.66)	
ECOG PS				0.483
0	41 (25.15)	15 (33.33)	26 (22.03)	
1	69 (42.33)	19 (42.22)	50 (42.37)	
2	28 (17.18)	6 (13.33)	22 (18.64)	
3	9 (5.52)	1 (2.22)	8 (6.78)	
X	16 (9.82)	4 (8.89)	12 (10.17)	
EGFR				0.202
Yes	42 (25.77)	14 (28.89)	28 (43.22)	
No	64 (39.26)	13 (31.11)	51 (23.73)	
NA	57 (34.97)	18 (40.00)	39 (33.05)	
Drug (TKI)				0.112
Erlotinib	137 (84.05)	34 (75.56)	103 (87.29)	
Gefitinib	26 (15.95)	11 (24.44)	15 (12.71)	
Line of treatment				0.614
1	37 (22.70)	11 (24.44)	26 (22.03)	
2	48 (29.45)	15 (33.33)	33 (27.97)	
≥3	78 (47.85)	19 (42.22)	59 (50.00)	

NA: not available

treatment with a TKI (platinum+paclitaxel, n=30; 23.81%), platinum + pemetrexed, n=28; 22.22%). No statistically significant differences were found in both clinical and demographic baseline characteristics among As-users and Non-As users (Table 1).

Effect of As

72.39% (n=118) of patients were As-users, while the remaining 27.61% (n=45) were non-As users.

The median PFS in the As-users was significantly lower than in the non-As users (84 days; 95% CI, 65-101 vs 221 days; 95% CI, 125-429) respectively (log rank p <0.0001; Figure 1).

A multivariate analysis was performed using the Cox proportional hazards model, comparing the relationship between PFS and the following variables: age, sex, ECOG PS, treatment line and use of As. The results were statistically significant for ECOG PS, treatment line and use of As, with a hazard ratio value for PFS of 1.79 (95% CI 1.42-2.24), 1.63 (95% CI 1.28-2.06) and 2.50 (95% CI 1.61-3.88) respectively (Table 2). After the results, a mathematical assumption of the model was made, where it was shown that it was not violated for alpha 0.05.

Effect of type of As

Of the 118 As-users, 72.03% received an IBP (n=85) while the remaining 27.97% (n=33) received an H2RA. Omeprazole was the most used As (n=67; 56.78%), followed by ranitidine (n=31; 26.27%) (Table 3).

The median PFS in patients with PPI vs H2RA was 84 days (95% CI, 61-101) vs 80.5 days (95% CI, 56-163), respectively, with no statistically significant differences between groups (Figure 2).

Best response reached and reason for discontinuation

The best response during treatment with TKI was stable disease in 23.93% (n=39) of the patients, partial response in 19.63% (n=32) and 1.84% (n=3) achieved complete response. The remaining 50.31% (n=82) presented disease progression. Comparing the best responses achieved by both groups, the proportion of patients with stable disease (31.11 vs 21.19%), partial response (28.89 vs 16.10%) and complete response (4.44 vs 0.85%) was superior in non-As users compared to As-users (Table 4).

Table 2. Multivariate Cox regression analysis of clinical variables evaluating the effect on PFS

Clinical variables	*Hazard ratio*	*95%CI*	*p value*
Age	0.9836	0.9667 - 1.001	0.0619
Sex	0.7441	0.5012 - 1.105	0.1427
ECOG PS	1.7866	1.4225 - 2.244	<0.0001
Treatment line	1.6280	1.2833 - 2.065	<0.0001
Acid suppression therapy	2.4983	1.6100 - 3.877	<0.0001

ECOG: Eastern Cooperative Oncology Group performance status, PFS: progression free survival, CI: confidence interval

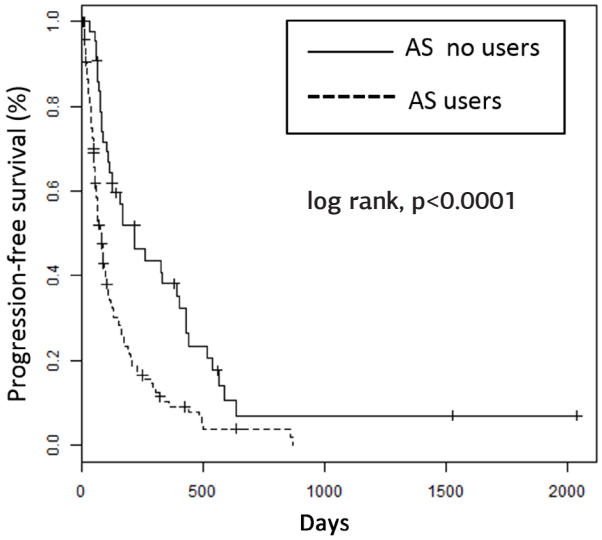

Figure 1. Kaplan Meier progression-free survival for As and non-As users.

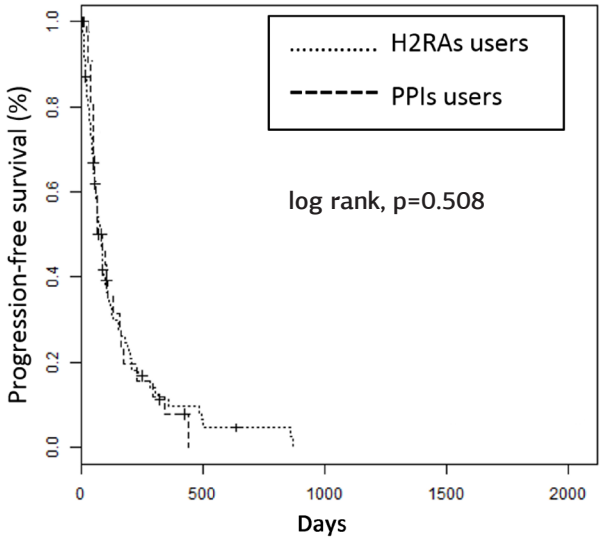

Figure 2. Kaplan Meier progression-free survival for PPIs and H2RAs users.

The reasons for discontinuation of TKI treatment included disease progression (85.89%, n=140), TKI toxicity or intolerance (7.98%, n=13) and only one patient discontinued treatment because of complete remission of disease. In As users, treatment discontinuation due to disease progression was 88.98% and due to toxicity or intolerance 6.78%. In non-As users the respective figures were 77.98% and 11.11% (p=0.162; Table 5).

Discussion

Acid suppressing medications are widely consumed by the general population to prevent gastrointestinal damage due to non steroidal anti inflammatory drugs (NSAIDs) and to treat gastroesophageal reflux, as well as gastric ulcers or infections by Helicobacter Pylori [15,16]. The need for gastrointestinal protection in patients treated with erlotinib was evidenced following a safety notification in 2009 about intestinal perforations associated with its use [17].

There is a high prevalence of As use in cancer patients [10,18,19] especially to treat gastric irritation derived from NSAIDs and dexamethasone.

Until recently, information about a possible interaction between erlotinib or gefitinib and As came mostly from randomized studies in healthy volunteers. In these studies, TKIs-AUC and Cmax decreased when co-administered with a PPI or a H2RA [11,13,14]. However, the clinical consequences of this interaction began to be investigated after the BR-21 trial. Hilton et al. carried out a retrospective analysis of the trial data, concluding that coadministration of As and erlotinib did not appear to have a significant impact on plasma drug levels or patient survival [20]. Due to these discrepancies, Chu et al. carried out a retrospective study following the line of Hilton et al. This study showed that antacids negatively affected the efficacy of erlotinib in both PFS (HR:1.83, 1.4 vs 2.3 months, p<0.001) and OS (HR:1.37, 12.9 vs 16.8 months, p=0.003) [21].

Subsequently, Zenke et al. carried out a retrospective study that included only patients with EGFR mutation treated with erlotinib or gefitinib, observing that As therapy did not have an adverse impact on median PFS (8.7 vs 10.7 months, p=0.13) and OS (20.1 vs 24.3 months, p=0.07) [22]. In the same year Kumarakulasinghe et al. confirmed the results of Zenke et al. obtaining similar results [23].

In our study, the concomitant use of As and erlotinib or gefitinib affected negatively the clinical results of TKIs in terms of PFS. As far as we know,

Table 3. Type of As used concomitantly with a TKI

As	*n (%)*
PPI	
Omeprazole	67 (56.78)
Pantoprazole	7 (5.93)
Esomeprazole	7 (5.93)
Rabeprazole	3 (2.54)
Lansoprazole	1 (0.85)
H2RA	
Ranitidine	31 (26.27)
Famotidine	2 (1.69)

Table 4. Best response achieved during treatment with TKI

Type of response	*Total n=163 n (%)*	*Non-As users n=45 n (%)*	*As users n=118 n (%)*	*p value*
Complete response	3 (1.84)	2 (4.44)	1 (0.85)	
Partial response	32 (19.63)	13 (28.89)	19 (16.10)	
Stable disease	39 (23.93)	14 (31.11)	25 (21.19)	0.028
Progression	82 (50.31)	14 (31.11)	68 (57.63)	
Unknown	7 (4.29)	2 (4.44)	5 (4.24)	

Table 5. Reasons for discontinuation of treatment with TKI

Reasons for discontinuation	*Total n=163 n (%)*	*Non- As users n=45 n (%)*	*As users n=118 n (%)*	*p value*
Progression of disease	140 (85.89)	35 (77.78)	105 (88.98)	
Toxicity-Intolerance	13 (7.98)	5 (11.11)	8 (6.78)	0.162
Complete remission	1 (0.61)	1 (2.22)	-	
Still under treatment	9 (5.52)	4 (8.89)	5 (4.24)	

this is the first European study to investigate the clinical impact of the interaction between AS and erlotinib or gefitinb including patients regardless of EGFR mutation state.

It must be taken into account that the activation of EGFR mutations confers a greater sensitivity to TKIs in NSCLC. This fact has been observed in cell lines with these mutations, that presented up to 10-50 times greater sensitivity to gefitinib [24,25]. Thus, as Zenke and Kumarakulasinghe indicated in their studies, a possible justification for their results would be that plasma levels of erlotinib and gefitinib when coadministered with As in patients with EGFR mutations may still be high enough to achieve an effective EGFR inhibition, despite the fact that the bioavailability is reduced.

This could explain, therefore, the results obtained both in our study and in the study of Chu et al., where the majority of patients included did not present EGFR mutations. These patients could be more sensitive to possible variations in TKI plasma levels. In addition, in our study population, As users had a lower percentage of treatment discontinuations due to intolerance-toxicity than the non users.

Regarding the different types of As, PPIs have a long duration of action, with 50-80% of basal gastric secretion inhibited after 24-h administration [26]. Since PPIs can maintain a high gastric pH for such a long period of time, to take PPIs and TKIs in different moments of the day would not avoid the interaction. On the other hand, it has been observed that when erlotinib is administered 2 hrs before or 10 hrs after administration of ranitidine, the AUC and Cmax for erlotinib is reduced by 15 and 17% respectively [27] vs 33 and 54% [13] when it does so concomitantly. These results led us to believe that H2RAs could be an alternative to PPIs in those patients who need to take an As and a TKI, with a lower impact on the absorption of TKI when the administration was performed in a stepwise dosing regime.

Regarding the type of As used, no significant differences on PFS were observed in our study. This can be explained because we could not differentiate, within patients with H2RAs, those who presented a concurrent or sequential pattern. The reason for choosing the 20% overlapping time between TKI and As was to have the possibility of comparing our results with those obtained by Chu et al., who used this value in their study [21].

Some limitations of our study should be acknowledged. We could not measure EGFR-TKIs serum concentration for the different groups because of its retrospective nature; the sample size was relatively small, especially in the non-As users group; and the long intervals between radiological evaluations prevented an accurate assessment of treatment responses. In addition, patients with EGFR mutation could not be compared to patients without mutation due to the small number of patients that presented it. Some confounding factors presented in the study are: patient compliance, over-the-counter use of As (which means a lack of prescription), or factors related to active substance (interpatient variability in absorption [28] and concomitant use of inhibitors or inducers of cytochrome P450 3A4, which can modify the exposure of both erlotinib and gefitinib in the body) [13,14].

Despite these limitations, the results obtained further open the debate about the use of As in NSCLC patients on treatment with erlotinib or gefitinib. Our results should be considered as exploratory, requiring large long-term prospective studies to confirm our findings and in which confounders are controlled for a better understanding of this interaction. It is also important to look for potential pharmacological strategies to eliminate this interaction and we must bear in mind that our results should not be extrapolated to other oral antineoplastics, many of which have weak base properties [10].

We could conclude that the possible interactions between TKIs and other drugs pose a significant challenge in the management of these patients. In addition, factors such as alcohol consumption, smoking and obesity are frequently associated with a higher prevalence of lung cancer and gastrointestinal diseases, triggering consumption of antacids that would lead to poor adherence to TKI therapy. Therefore, it is important to re-evaluate the indication and necessity of therapy with As when a patient is being treated with erlotinib or gefitinib, weighing the benefits and risks of a possible discontinuation, since the clinical relevance of this interaction seems increasingly clear.

Conclusion

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Conflict of interests

The authors declare no conflict of interests.

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