Effect of acid suppressants on the efficacy of tyrosine kinase inhibitors in patients with epidermal growth factor receptor-mutated non-small-cell lung cancer

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Abstract. This retrospective study was conducted to evaluate whether oral acid suppressant (AS) therapy is associated with decreased efficacy of gefitinib and erlotinib, particularly in patients with mutated epidermal growth factor receptor (EGFR). A total of 46 consecutive patients with pathologically confirmed non-small-cell lung cancer (NSCLC), who were treated with tyrosine kinase inhibitors (TKIs) in two tertiary hospitals between September, 2005 and May, 2013, were retrospectively analyzed. Of the 46 patients, 11 received AS treatment. As regards age, gender, smoking history, performance status, histology of lung cancer, clinical stage, body surface area (BSA) and type of EGFR mutation, there were no statistically significant differences between patients with and those without AS treatment. There was no statistically significant difference in progression-free survival (PFS) or overall survival (OS) between the two groups of patients (P=0.296 and 0.613, respectively). As regards the relative dose of TKI/BSA and survival in patients with and those without AS treatment, there were no statistically significant differences in PFS and OS between the two groups of patients. Our study indicates that AS treatment may not compromise TKI efficacy (gefitinib or erlotinib) in NSCLC patients with mutated EGFR. Prospective studies and large-scale confirmation studies investigating the effect of AS co-administration with TKIs in patients with mutated EGFR may be meaningful in clinical practice.

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Introduction

As gastroesophageal reflux disease is highly prevalent among the elderly (1) and peptic ulcer and diffuse erosive gastritis are not uncommon among cancer patients who are under severe mental stress (2), acid suppressant (AS) therapy with a histamine type-2 receptor antagonist (H2RA) and/or a proton pump inhibitor (PPI) are usually prescribed in these patients. Although not common, dyspepsia and abdominal discomfort are two of the possible adverse effects of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) (3). Therefore, drug interactions between AS and TKIs are a clinical issue in the management of patients treated with TKIs. During preclinical evaluation, one of the TKIs, erlotinib, was found to exhibit pH-dependent solubility, with a dissociation constant of 5.4 (3). This pH-dependent solubility was reflected in a study that compared its plasma concentrations in healthy subjects who were or were not receiving AS therapy (4). In addition, the H2RA ranitidine decreased the median area under the curve (AUC) of erlotinib by 33% (3). Recently, two clinical evaluations of the interaction between AS therapy and erlotinib have been reported, and they reported opposing findings, namely that AS therapy was associated with decreased erlotinib efficacy (5) and that there was no such an association (6). These studies included patients with unknown EGFR mutation status and only evaluated the efficacy of erlotinib therapy (5,6). On the other hand, however, Ter Heine *et al* reported lower than expected erlotinib trough concentrations in a patient who received pantoprazole, an intravenous PPI, but this discrepancy was not observed when oral pantoprazole was prescribed (7). The EGFR mutation status was not described in that case report.

In the present study, we investigated whether oral AS therapy is truly associated with decreased efficacy of gefitinib and erlotinib, particularly in patients with mutated EGFR.

Patients and methods

Patients. A total of 46 consecutive patients with pathologically confirmed non-small-cell lung cancer (NSCLC), who were treated with TKIs at the Ryugasaki Saiseikai General Hospital

Table I. Characteristics of EGFR-mutated NSCLC patients with or without acid suppressant (AS) treatment.

Characteristics	With AS (n=11)	Without AS (n=35)	P-value
Age, years [median (range)]	74 (52-88)	77 (52-89)	0.708
Gender			1.000
Male	2	9	
Female	9	26	
Smoking history			0.559
Never smokers	11	31	
Current/former smoker	0	4	
ECOG performance status			0.433
0-1	10	31	
2-4	1	4	
Histology			0.138
Adenocarcinoma	9	34	
Others	2	1	
Stage			1.000
IIIA	2	8	
IV	9	27	
Body surface area, m^2 [median (range)]	1.42 (1.11-1.86)	1.41 (1.17-1.83)	0.588
EGFR mutation			0.133
Exon 19 deletion	9	15	
Exon21 L858R	2	18	
Others	0	2	

EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

and the Mito Medical Center between September, 2005 and May, 2013, were retrospectively analyzed. The histopathological diagnoses were performed according to the World Health Organization classification system (8) and the patients were staged according to the Union for International Cancer Control tumor-node-metastasis staging system (9).

The patient characteristics and the treatment efficacy and safety were evaluated using patient data extracted from the database of each participating institution. Tumor response was classified as complete response, partial response, stable disease, progressive disease or not evaluable, according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (10).

We next evaluated the TKI dose prescribed and patient survival, taking body surface area (BSA) into consideration. Briefly, we defined relative dose of TKI as the prescribed dose divided by the full dose (gefitinib, 250 mg; erlotinib, 150 mg). In addition, we divided the relative dose of TKI by BSA and evaluated the association between relative dose of TKI/BSA and survival of patients with or without AS treatment.

The present retrospective study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan. Ethical approval of this study was obtained from the Institutional Review Board of the Ryugasaki Saiseikai Hospital (Ryugasaki, Japan).

Statistical analysis. Statistical significance was determined using the Mann-Whitney U test and the Chi-square test.

Survival time was calculated from the day of TKI initiation to death or last follow-up. The survival rate was analyzed with the Kaplan-Meier method and comparisons were performed using the log-rank test. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. During the study period, a total of 46 patients were treated with TKIs (29 with gefitinib and 17 with erlotinib). Of the 46 patients, 11 received AS treatment and 35 did not. The characteristics of EGFR-mutated NSCLC patients with or without AS treatment are summarized in Table I. As regards age, gender, smoking history, performance status, cancer histology, clinical stage, BSA and type of EGFR mutation, there were no statistically differences between the two groups.

TKI therapy. The characteristics of TKI therapy are shown in Table II. There were no statistically significant differences in terms of TKI prescribed, dose reduction, prior therapy and relative dose of TKI/BSA between patients with and those without AS treatment.

Survival analysis. There were no statistically significant differences in PFS between the 11 patients with AS and the 35 patients without AS treatment (Fig. 1) (P=0.296). OS also did not differ significantly between the two groups (Fig. 2) (P=0.613).

Table II. Prescribed TKIs, dose reduction, prior therapy and % of initial dose/BSA in patients with or without AS treatment.

Variables	With AS	Without AS	P-value
Prescribed TKI (patient no.)			0.501
Gefitinib	8	21	
Erlotinib	3	14	
TKI dose reduction			0.2419
Present	2	13	
Absent	9	22	
Prior therapy			0.282
Present	4	14	
Absent	7	21	
% of initial dose/BSA (%/m^2)			0.471
Median (range)	70.4 (48.9-90.1)	70.9 (47.5-85.5)	

TKI, tyrosine kinase inhibitor; BSA, body surface area; AS, acid suppressant.

Table III. Relative dose of TKI/BSA and survival in patients with or without AS treatment.

	Survival		
Relative dose of TKI[a]/BSA	With AS	Without AS	P-value
≥70 (%/m^2)			
Number of patients	5	17	
PFS, months (range)	24 (1-NA)	18 (2-NA)	0.959
OS, months (range)	44 (1-NA)	34 (17-NA)	0.342
<70 (%/m^2)			
Number of patients	6	18	
PFS, months (range)	6 (1-NA)	13 (2-29)	0.959
OS, months (range)	4 (1-NA)	22 (11-NA)	0.361

[a]Prescribed dose/full dose (gefitinib, 250 mg; erlotinib, 150 mg). TKI, tyrosine kinase inhibitor; BSA, body surface area; AS, acid suppressant; PFS, progression-free survival; OS, overall survival; NA, not applicable.
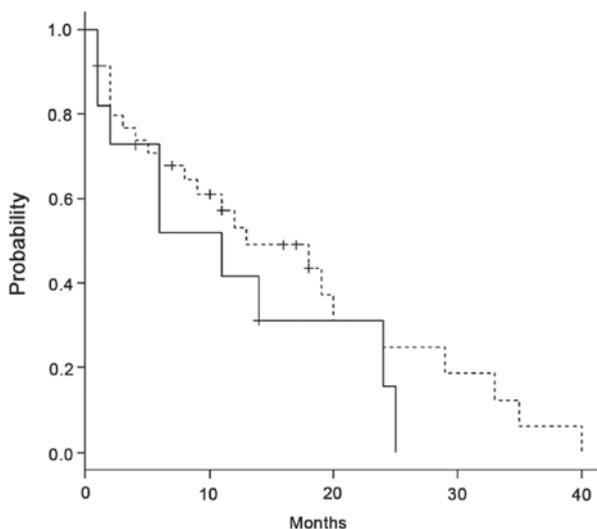

Figure 1. Progression-free survival curves of epidermal growth factor receptor-mutated non-small-cell cancer patients with or without acid supressant (AS) treatment. Solid line, patients with AS; dashed line, patients without AS.
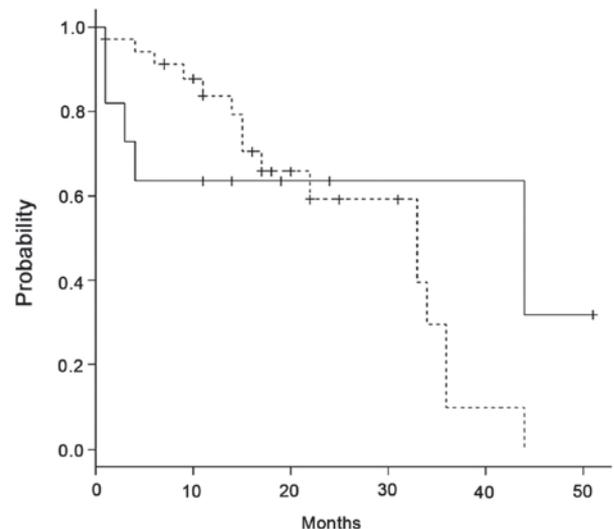

Figure 2. Overall survival curves of epidermal growth factor receptor-mutated non-small-cell cancer patients with or without acid supressant (AS) treatment. Solid line, patients with AS; dashed line, patients without AS.

Association between relative dose of TKI/BSA and survival. We next evaluated the association between the relative dose of TKI/BSA and survival in NSCLC patients with or without AS treatment. The median of the relative dose of TKI/BSA in patients with AS and those without AS was 70.4 and 70.9 %/m^2, respectively (Table II); therefore, we performed the analysis in patients with a relative dose of TKI/BSA of ≥70 and in those with a relative dose of TKI/BSA of <70 %/m^2. There were no statistically significant differences in PFS and OS between the two groups of patients (Table III).

Discussion

In the present study, we evaluated whether oral AS therapy is truly associated with decreased efficacy of gefitinib and erlotinib, particularly in patients with mutated EGFR. Our results demonstrated that oral AS therapy is not associated with decreased efficacy of gefitinib and erlotinib in patients with mutated EGFR, which was inconsistent (5) or consistent (6) with previous studies. Chu *et al* (5) reported that gastric acid suppression was associated with decreased erlotinib efficacy in NSCLC patients. That retrospective study included 507 patients with advanced NSCLC, but there were 487 patients with unknown EGFR mutation status. By contrast, Hilton *et al* (6) reported that the co-administration of AS treatment with erlotinib did not appear to exert a significant effect on the median plasma drug levels or the outcome. The study evaluated pharmacokinetics and survival in the patients of a phase III clinical trial (BR.21), but there was no information regarding the association among AS treatment, EGFR mutation status and patient survival (6). Although it is clear that AS administration may affect the absorption of erlotinib in an experimental setting, it is uncertain whether the decreased erlotinib efficacy associated with AS in the study by Chu *et al* (5) can be generalized when AS agents are prescribed for oral use, or when other TKIs, such as gefitinib, are prescribed in patients with mutated EGFR. This inconsistence in the results may be attributed to a number of possible reasons, such as the difference in EGFR mutation status, difference in BSA of the patients, difference in the AS agent prescribed, and different ethnicities. All our patients had mutated EGFR, the median BSA of the patients was 1.41-1.42 m^2, all the patients had received oral AS treatment, and all our patients were Asians and Caucasians similar to the study by Chu *et al* (5).

It is well known that the association between the maximum tolerated dose (MTD) and recommended dose (RD) in erlotinib and gefitinib treatment may be associated with this inconsistency. The RD of gefitinib (250 mg/day) for NSCLC is only one-third of its MTD, whereas the RD used for erlotinib (150 mg/day) is its MTD (11,12). Cigarette smoking is a well-known factor that may alter erlotinib plasma levels (13). In our study, there was no difference in smoking status between patients with and those without AS treatment. In addition, no patients were smoking during the TKI administration. Another explanation for the inconsistency may be that it reflects the presence of comorbidities where AS use was indicated, such as aspirin for cardiovascular disease, dexamethasone for symptomatic NSCLC, gastroesophageal reflux or treatment for duodenal or gastric ulcers. Taking this evidence into

consideration, we hypothesized that, in patients with mutated EGFR, decreased AUC by AS therapy may exert a relatively smaller effect on TKI efficacy compared with that in patients with wild-type EGFR, i.e., prevalence of an EGFR mutation may allow a significantly lower than standard TKI dose to be effective, thereby circumventing the reduced TKI absorption caused by AS therapy, as suggested by Yeo *et al* in a study on erlotinib therapy (14).

The main limitation of our study is due to its retrospective design and the small sample size. In addition, there were no data on pharmacokinetics and its effect on treatment efficacy. In addition, no data are available on whether AS treatment decreases TKI serum levels in Japanese patients. If so, it is not known whether the serum level is decreased below what would be clinically efficient. However, despite these limitations, the difference in our outcomes compared with those of previous studies on erlotinib therapy may be of clinical value when administering TKIs and AS therapy in NSCLC patients with mutated EGFR.

In conclusion, our study suggests that AS treatment may not compromise TKI efficacy in patients with mutated EGFR. Prospective studies and large-scale confirmation studies investigating the effect of AS and TKI co-administration in NSCLC patients with mutated EGFR may be meaningful in clinical practice.

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