Gender-Based Impact of Epidermal Growth Factor Receptor Mutation in Patients With Nonsmall Cell Lung Cancer and Previous Tuberculosis

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Abstract: The association between tuberculosis (TB) and lung cancer is well known. However, carcinogenesis of TB and its connection with epidermal growth factor receptor (EGFR) mutation remains unclear. This study aimed to determine this connection to see if TB can affect the outcome of patients with lung cancer.

This is a retrospective cohort study of patients with lung cancer receiving EGFR-tyrosine kinase inhibitors (TKIs) between 1996 and 2010 using the National Health Insurance Research Database of Taiwan. Because therapeutic response was required to apply EGFR-TKIs for >90 days, only patients with a follow-up of >120 days were studied and a responder was defined as intake of EGFR-TKIs >90 days. Predictors of EGFR-TKI response and survival were identified using logistic and Cox regression analyses, respectively.

There were 8265 patients analyzed, including 6073 (73.5%) EGFR-TKI responder and 2192 (26.5%) nonresponder. A history of TB was found in 1.2% and 1.8% of the 2 groups, respectively. Comparing to male with pulmonary TB history, female with or without pulmonary TB history and male without pulmonary TB history all had a better EGFR-TKI response and 1-year progression-free survival (PFS). Gender and TB history were not independent prognostic factors of 2-year overall survival. The findings were similar in the subpopulation without chronic obstructive pulmonary disease, malignancies other than lung cancer, and low-income status.

INTRODUCTION

Lung cancer is the leading cause of mortality in all patients with cancer, accounting for 14% of newly diagnosed cancer cases and 26% to 28% of all cancer deaths in the United States. One meta-analysis shows that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) prolong progression-free survival (PFS) (hazard ratio [HR] 0.43 [0.38–0.49]), but not overall survival (OS) (HR 1.01 [0.87–1.18]), in patients with sensitive EGFR mutation. The frequency of sensitive EGFR mutation is found in approximately 10% of Caucasians with nonsmall cell lung cancer (NSCLC) and >50% of Asian patients. Patients with female sex, adenocarcinoma histology, never-smoking status, and Asian ethnicity are considered to have a high prevalence of EGFR mutation according to the Iressa Pan-Asia Study (IPASS) trial and the molecular epidemiology study of EGFR mutations in Asian patients with advanced NSCLC of adenocarcinoma (PIONEER) trial.

Tuberculosis (TB) is a global disease affecting one third of the world’s population. Several prospective and retrospective studies have demonstrated the association between lung cancer and pulmonary TB. One possible mechanism of carcinogenesis in patients with pulmonary TB is chronic inflammation, as proposed by Virchow in 1863. Chronic inflammation may lead to scar formation, resulting in dysplasia and scar carcinoma of the lungs. An experimental study in mice has not only shown a causal link between pulmonary TB and lung carcinogenesis but also established a genetic model for further analysis of the carcinogenic mechanisms activated by Mycobacterium tuberculosis.

Recent reports regarding the impact of TB on the outcome of patients with lung cancer are contradictory; some show increased mortality in patients with lung cancer, whereas others reveal improved survival in patients with NSCLC. In addition, little is known about the impact of pulmonary TB on EGFR mutation and PFS. A recent report from Taiwan focusing on a small number of patients with lung adenocarcinoma (n = 275) reveals that patients with radiographic evidence compatible with old pulmonary TB have a higher incidence of EGFR mutation than those without (OR [odds ratio]: 1.83 [0.92–3.62]). However, the association is not found in patients with female sex, adenocarcinoma histology, never-smoking status, and Asian ethnicity.
patients with a clinical history of pulmonary TB. Large cohort studies are needed to clarify these issues.

As a mandatory universal health insurance program offering comprehensive medical care coverage, the National Health Insurance (NHI) of Taiwan covers up to 99% of residents in Taiwan. With a longitudinal follow-up of >22 million patients, the National Health Insurance Research Database (NHIRD) provides a very suitable research material to explore the long-term interaction between communicable and noncommunicable diseases. Moreover, the incidences of sensitive EGFR mutation (51.4%–58.4%) and pulmonary TB are high in Taiwan. Thus, this study was conducted using the NHIRD to investigate the correlation between pulmonary TB history and sensitive EGFR mutation, and clarify the impact of pulmonary TB history on PFS and OS of patients with lung cancer. Because the smoking status was not available in the NHIRD, smoking-associated comorbidities including chronic obstructive pulmonary disease (COPD), malignancies other than lung cancer, and low-income status were used as a proxy of smoking.

MATERIALS AND METHODS

Ethical Approval

The Institutional Review Board of the National Taiwan University Hospital, Taipei, Taiwan, approved the study (NTUH REC: 20121201W) and waived the need for informed consent because of the retrospective design and use of an encrypted database.

Case Selection

Patients with lung cancer were identified by a compatible diagnosis (International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] code 162) from the Registry of Catastrophic Illness Patients Database, a subset of the NHIRD. To apply for this registry, histological confirmation is obligated. The index date was defined as the initial date the patient applying for this registry for lung cancer.

The EGFR-TKIs included gefitinib and erlotinib. The prescription duration of individual EGFR-TKI was converted from the claims data according to the defined daily doses. These drugs required preaudit approval by the NHI administration and second-line therapy, only benefited patients with lung adenocarcinoma after the first-line treatment with chemotherapy, except for a third-line indication of erlotinib for patients with NSCLC. The approval was reaudited every 90 days and reissued only to those with favorable response to EGFR-TKIs, that is, stable disease or partial or complete response. Thus, patients who died within 120 days after starting the EGFR-TKIs were excluded to ensure that EGFR-TKIs response was determined. Patients who discontinued EGFR-TKIs within 90 days were classified as EGFR-TKI nonresponders; others were classified as EGFR-TKI responders. The selection processes were shown in Figure 1.

The association of pulmonary TB history and other comorbidities on EGFR-TKI response were studied among patients with lung cancer. All of the selected cases were followed up until December 31, 2010, announced death, or loss to follow-up (canceled health insurance prior to December 31, 2010).

Definition of Pulmonary TB

Pulmonary TB was identified according to a previous publication. Briefly, there was at least 2 ambulatory visits or 1 inpatient record with a compatible diagnosis (ICD-9-CM codes 010–012 and 018, and A-codes A020, A021), with at least 1 prescription consisting of ≥3 anti-TB drugs (isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, and second-line drugs, including protonamide, terizidone, streptomycin, kanamycin, cycloserine, aminosalicylic acid, and fluoroquinolones). Moreover, there were prescriptions of at least 2 anti-TB drugs simultaneously for not <120 days within a period of 180 days.

Comorbidities

COPD, diabetes mellitus, end-stage renal disease (ESRD), liver cirrhosis, pneumoconiosis, autoimmune diseases, organ transplantation, acquired-immunodeficiency syndrome, and other malignancies were identified according to a previous publication. The low-income group was identified from the Catastrophic Illness Patients Database, a subset of the NHIRD. To apply for this registry, patients with a clinical history of pulmonary TB. Large cohort studies are needed to clarify these issues.

Statistical Analysis

Intergroup difference was compared using the $t$ test or Mann–Whitney U test for continuous variables based on their normality, and the $\chi^2$ test or Fisher exact test for categorical variables, as appropriate. Logistic regression analyses were performed to evaluate the impact of age, gender, comorbidities, income status, and a history of pulmonary TB on EGFR mutation.
On the basis of a previous study in Asia showing that the median PFS and OS in patients receiving gefitinib were 5.7 and 18.6 months, respectively, curves of 1-year PFS and 2-year OS (from the date of registry of lung cancer) for each variable were generated using the Kaplan–Meier method and compared by using the log-rank test. PFS was defined as the interval between the commencement and discontinuation of EGFR-TKIs under the assumption that patients without progression of disease would keep on EGFR-TKI therapy. Cox proportional hazards regression analysis was then applied to identify the independent prognostic factors. While conducting multivariate analyses, potential interactions between variables were checked and all variables with P ≤ 0.1 in univariate analysis were included. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS, v. 18.0; SPSS Inc, Chicago, IL).

Sensitivity Analysis
Because smoking is associated with both TB and lung cancer,29,30 sensitivity analysis focusing on a predominantly nonsmoking subpopulation, patients without COPD, malignancies other than lung cancer, and low-income status, was performed to minimize the confounding effect of smoking.

RESULTS
Patient Characteristics
From 1996 to 2010, a total of 112,356 patients with lung cancer were identified with 12,085 who received erlotinib and/ or gefitinib (Figure 1). Among them, 8265 patients, including 6073 (73.5%) who received gefitinib, had a follow-up duration of >120 days after the start of EGFR-TKI therapy. Among them, 6073 (73.5%) who received EGFR-TKIs for >90 days and were classified as EGFR-TKI responders. The remaining 2192 (26.5%) were classified as nonresponders.

The comparisons of clinical characteristics between the EGFR-TKI responders and nonresponders were shown in Table 1. The mean age was 61.6 ± 12.0, with 44.8% aged >65 years. There was no age difference between the 2 groups. By gender, 53.0% were female. The most common underlying comorbidities were diabetes mellitus (16.1%), COPD (8.2%), and malignancies other than lung cancer (5.2%). The EGFR-TKI responders were more likely to be female (56.3% vs 43.8%, P < 0.001), less likely to have a history of pulmonary TB (1.2% vs 1.8%, P = 0.045), COPD (7.0% vs 11.3%, P < 0.001), and malignancies other than lung cancer (4.9% vs 6.1%, P = 0.023), and of low-income status (0.7% vs 1.1%, P = 0.036).

Predictors of Response to EGFR-TKI
Univariate analysis revealed that female gender was associated with good response to EGFR-TKI, whereas COPD, malignancies other than lung cancer, pulmonary TB history, and low-income status were associated with poor response (Table 2). In male patients with lung cancer, the proportion of good EGFR-TKI response was 52.7% in patients with pulmonary TB history and 68.6% in those without pulmonary TB history, and 89.5% and 78.0% in female patients with lung cancer, respectively. Because of the presence of interaction between gender and pulmonary TB history, a new variable, gender and TB history, was introduced to replace the 2 variables—gender and pulmonary TB history.

In a comparison of male with pulmonary TB history in multivariate logistic regression analysis, female with pulmonary TB history (OR: 7.09 [2.28–22.05]), female without pulmonary TB history (OR: 2.86 [1.79–4.55]), and male without pulmonary TB history (OR: 1.80 [1.13–2.87]), all had a significantly better EGFR-TKIs response (Table 2). Other independent predictors of EGFR-TKI response included COPD (OR: 0.68 [0.57–0.80]), malignancies other than lung cancer (OR: 0.76 [0.61–0.94]), and low income (OR: 0.58 [0.35–0.97]).

### TABLE 1. Patient Characteristics Based on EGFR-TKI Treatment Response

| Variables                | All (n = 8265) | Responder (n = 6073) | Nonresponder (n = 2192) | P Value |
|--------------------------|---------------|----------------------|-------------------------|---------|
| Female                   | 4377 (53.0)   | 3418 (56.3)          | 959 (43.8)              | <0.001  |
| Age                      | 61.6 ± 12.0   | 61.6 ± 11.8          | 61.7 ± 12.6             | 0.595   |
| Age ≥65                  | 3703 (44.8)   | 2690 (44.3)          | 1013 (46.2)             | 0.121   |
| Comorbidity              | 2191 (26.5)   | 1530 (25.2)          | 661 (30.2)              | <0.001  |
| Diabetes mellitus        | 1330 (16.1)   | 966 (15.9)           | 364 (16.6)              | 0.445   |
| COPD                     | 675 (8.2)     | 428 (7.0)            | 247 (11.3)              | <0.001  |
| Other malignancies       | 429 (5.2)     | 295 (4.9)            | 134 (6.1)               | 0.023   |
| CTD                      | 48 (0.6)      | 31 (0.5)             | 17 (0.8)                | 0.161   |
| ESRD                     | 11 (0.05)     | 9 (0.1)              | 2 (0.1)                 | 0.531   |
| Liver cirrhosis          | 4 (0.05)      | 2 (0.1)              | 2 (0.03)                | 0.287   |
| Transplantation          | 1 (0.01)      | 1 (0.02)             | 0 (0)                   | 0.548   |
| AIDS                     | 1 (0.01)      | 1 (0.02)             | 0 (0)                   | 0.548   |
| Ventilator               | 4 (0.05)      | 3 (0.05)             | 1 (0.05)                | 0.945   |
| Low income               | 66 (0.8)      | 41 (0.7)             | 25 (1.1)                | 0.036   |
| Tuberculosis history     | 112 (1.4)     | 73 (1.2)             | 39 (1.8)                | 0.045   |
| ≥1 episode               | 3 (0.04)      | 2 (0.03)             | 1 (0.05)                | 0.789   |

AIDS = acquired-immunodeficiency syndrome, COPD = chronic obstructive pulmonary disease, CTD = connective tissue disease, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, ESRD = end-stage renal disease.

Data are presented as number (%) or mean ± standard deviation. One patient can have multiple comorbidities.
Prognostic Factors of 1-Year PFS

Univariate Cox regression analysis revealed that prognostic factors of 1-year PFS included gender and TB history, comorbidity (including COPD and diabetes mellitus), and low-income status (Table 3). The 1-year PFS was best in female with pulmonary TB history, followed by female without pulmonary TB history and male without pulmonary TB history, and was worst in male with pulmonary TB history. (P < 0.001, by log-rank test) (Figure 2A).

In multivariate Cox regression analysis, female with pulmonary TB history (HR: 0.41 [0.26–0.65]), female without pulmonary TB history (HR: 0.61 [0.48–0.79]), and male pulmonary TB history (HR: 0.40 [0.25–0.63]) were identified as independent predictors of 1-year PFS.

### TABLE 2. Univariate and Multivariate Logistic Regression Analysis for Predicting Response to ESRD-TKI

| Variable                         | No. of Cases | Percent of Responder | Univariate OR 95% CI P Value | Multivariate OR 95% CI P Value |
|----------------------------------|--------------|----------------------|-----------------------------|--------------------------------|
| Sex: female vs male              | 4377/3888    | 78.1/68.3            | 1.66 1.50–1.83 <0.001       |                                 |
| TB history: yes vs no            | 112/8153     | 65.2/73.6            | 0.67 0.45–0.99 0.047        |                                 |
| Gender and TB history            |              |                      |                             |                                 |
| Male with pulmonary TB history   | 74           | 52.7                 | Reference group             |                                 |
| Male without pulmonary TB history| 3814         | 68.6                 | 1.96 1.24–3.11 0.004        | 1.80 1.13–2.87 0.013            |
| Female without pulmonary TB history | 4339       | 78                   | 3.18 2.–5.05 <0.001         | 2.86 1.79–4.55 <0.001           |
| Female with pulmonary TB history | 38           | 89.5                 | 7.63 2.46–31.66 <0.001      | 7.09 2.28–22.05 0.001           |
| Age: ≥65 vs <65 y                |              |                      |                             |                                 |
| Comorbidity: yes vs no           | 112/8153     | 63.4/74.4            | 0.60 0.51–0.70 <0.001       | 0.68 0.57–0.80 <0.001           |
| Diabetes mellitus: yes vs no     | 1330/6935    | 72.6/73.6            | 0.95 0.83–1.08 0.445        |                                 |
| CTD: yes vs no                   | 48/8217      | 64.6/73.5            | 0.66 0.36–1.19 0.165        |                                 |
| Liver cirrhosis: yes vs no       | 48/8261      | 50.0/73.5            | 0.56 0.51–2.56 0.308        |                                 |
| Ventilator: yes vs no            | 48/8261      | 75.0/73.5            | 1.08 0.11–10.42 0.945       |                                 |
| Other malignancies: yes vs no    | 429/7836     | 68.8/73.7            | 0.78 0.64–0.97 0.023        | 0.76 0.61–0.94 0.010            |
| Low income: yes vs no            | 66/8199      | 62.1/73.6            | 0.59 0.35–0.97 0.038        | 0.58 0.35–0.97 0.036            |

AIDS = acquired-immunodeficiency syndrome, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CTD = connective tissue disease, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, OR = odds ratio, TB = tuberculosis.

### TABLE 3. Multivariate Cox Proportional Hazard Regression Analysis for 1-y PFS

| Variable                             | PFS Rate (%) | Univariate Cox Regression | Multivariate Cox Regression |
|--------------------------------------|--------------|---------------------------|----------------------------|
|                                      | Yes          | No                        | HR 95% CI P Value          | HR 95% CI P Value          |
| Gender and TB history                |              |                           |                            |                            |
| Male with pulmonary TB history       | 13.5         | 21.1                      | Reference group            | Reference group            |
| Male without pulmonary TB history    | 17.7         | 23.9                      | 0.75 0.58–0.96 0.02        | 0.78 0.61–1.00 0.051       |
| Female without pulmonary TB history  | 24.1         | 17.8                      | 0.58 0.45–0.74 <0.001      | 0.61 0.48–0.79 <0.001      |
| Female with pulmonary TB history     | 31.6         | 21.0                      | 0.40 0.25–0.63 <0.001      | 0.41 0.26–0.65 <0.001      |
| Age ≥65 y                            | 20.3         | 21.7                      | 1.05 1.00–1.10 0.052       | 1.08 1.01–1.15 0.021       |
| Comorbidity                          | 18.5         | 22.0                      | 1.14 1.08–1.20 <0.001      | 1.12 1.01–1.24 0.027       |
| COPD                                 | 15.4         | 21.6                      | 1.26 1.16–1.37 <0.001      |                            |
| Diabetes mellitus                    | 18.6         | 21.5                      | 1.09 1.02–1.16 0.014       |                            |
| Connective tissue disease            | 25.0         | 21.1                      | 0.97 0.70–1.34 0.830       |                            |
| Liver cirrhosis                      | 0            | 21.1                      | 2.39 0.90–6.38 0.081       |                            |
| Transplantation                      | 100          | 21.1                      | 0.50 0.00–58.38 0.405      |                            |
| AIDS                                 | 0            | 21.1                      | 1.90 0.27–13.52 0.519      |                            |
| Ventilator                           | 0            | 21.1                      | 1.65 0.62–4.41 0.315       |                            |
| End-stage renal disease              | 0            | 21.1                      | 1.67 0.92–3.02 0.089       |                            |
| Other malignancy                     | 21.9         | 21.0                      | 1.04 0.94–1.17 0.439       |                            |
| Low income                           | 7.6          | 21.1                      | 1.47 1.14–1.89 0.003       | 1.50 1.17–1.94 0.002       |

AIDS = acquired-immunodeficiency syndrome, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, OR = odds ratio, PFS = progression-free survival, TB = tuberculosis.

The numbers in the “Yes” and “No” columns represent the 1-y PFS rate among patients with and without the corresponding characteristic listed in the “Variable” column, respectively.
without pulmonary TB history (HR: 0.78 [0.61–1.00]) all had a significantly better 1-year PFS than male with pulmonary TB history. The presence of comorbidity (HR: 1.08 [1.01–1.15]), COPD (HR: 1.13 [1.02–1.24]), and low income (HR: 1.50 [1.17–1.93]) were independent prognostic factors of 1-year PFS.

Prognostic Factors of 2-Year OS

Univariate Cox regression analysis revealed that EGFR-TKI response, gender and TB history, age ≥65 years, presence of comorbidity, presence of COPD or ESRD, and low-income status were associated with 2-year OS (Table 4; Figure 2B and C).

In multivariate Cox regression analysis, independent prognostic factors of 2-year OS included EGFR-TKI response (HR: 0.59 [0.55–0.64]), age ≥65 years (HR: 1.23 [1.14–1.33]), ESRD (HR: 3.48 [1.56–7.75]), malignancies other than lung cancer (HR: 1.43 [1.22–1.66]), and low-income status (HR: 1.75 [1.24–2.46]). Although being a significant predictor in univariate analysis, gender and TB history was not an independent prognostic factor for 2-year OS (Table 4).

Sensitivity Analysis

Sensitivity analysis was performed on 7140 (86.4%) patients without COPD, malignancies other than lung cancer, and low income. Interaction between gender and pulmonary TB
that the impact of pulmonary TB history on EGFR-TKI observed on the 1-year PFS. Third, sensitivity analysis reveals patients but better response in female patients. The different response to EGFR-TKIs. Second, a history of pulmonary TB is the "Variable" column, respectively.

The numbers in the "Yes" and "No" columns represent the 2-y OS rate among patients with and without the corresponding characteristic listed in the "Variable" column, respectively.

### DISCUSSION

This is the first nationwide population-based cohort study to investigate the associations between sensitive EGFR mutation and a history of pulmonary TB in patients with lung cancer. The present study has 3 major findings. First, similar to the previous studies,4,5,31 the clinical response to EGFR-TKIs in sensitivity analysis leads to granuloma formation, fibrosis, and even dysplasia with scar cancer are considered as 2 possible mechanisms in carcinogenesis from TB.13

Inflammation is a critical component of tumor progression. It is now becoming clear that the tumor microenvironment, which is largely manipulated by inflammatory cells via cytokines and chemokines, fosters proliferation, survival, and migration.12

The most common chronic pulmonary infection is TB. Two retrospective studies from China show that pulmonary TB increases the risk of lung cancer, with a HR of 6.7 to 13 in the first 5 years after TB,9,10 which remains significant after adjustments for smoking and other confounding factors. Another 2 population cohort studies in Taiwan that includes >4000 patients have similar findings.9,11 TB-related chronic inflammation leads to granuloma formation, fibrosis, and even dysplasia with scar formation. Uncontrolled inflammations with cell dysplasia and scar cancer are considered as 2 possible mechanisms in carcinogenesis from TB.13

There are several reports about the connection between chronic inflammation and EGFR mutation. One report mentions that oxidant-induced goblet cell metaplasia in human airway epithelium leads to EGFR activation.30 Another report shows nitric oxide-induced epidermal growth factor-dependent phosphorylation in A431 tumor cells.35 It has also been reported that TB increases the expression of epiregulin, which correlates with the invasive properties on EGFR-mutant cells.14,36 A recent retrospective report from Taiwan has found a possible association between old pulmonary TB and sensitive EGFR mutation, especially exon 19 deletions.18 However, in this study, the diagnosis of pulmonary TB is simply based on radiographic

### TABLE 4. Multivariate Cox Proportional Hazard Regression Analysis for 2-y OS

| Variable                           | OS Rate (%) | Univariate Cox Regression | Multivariate Cox Regression |
|------------------------------------|-------------|---------------------------|-----------------------------|
| EGFR-TKI responder                 |             |                           |                             |
| Gender and TB history              |             |                           |                             |
| Male with pulmonary TB history     | 57.1        | 0.58                      | 0.54–0.63                   | <0.001                      | 0.59 | 0.55–0.64 | <0.001 |
| Male without pulmonary TB history  | 41.4        | Reference group           |                             |                             |      |          |        |
| Female without pulmonary TB history| 49.3        | 0.79                      | 0.56–1.10                   | 0.162                       |      |          |        |
| Female with pulmonary TB history   | 54.2        | 0.48                      | 0.48–0.95                   | 0.022                       |      |          |        |
| Age ≥65 y                          | 47.6        | 1.26                      | 1.17–1.36                   | <0.001                      | 1.24 | 1.15–1.34 | <0.001 |
| Comorbidities                      | 47.0        | 1.21                      | 1.12–1.31                   | <0.001                      |      |          |        |
| COPD                               | 47.8        | 1.14                      | 1.00–1.30                   | 0.050                       |      |          |        |
| Diabetes mellitus                  | 48.5        | 1.13                      | 1.02–1.24                   | 0.021                       |      |          |        |
| Connective tissue disease          | 44.8        | 1.17                      | 0.72–1.92                   | 0.523                       |      |          |        |
| Liver cirrhosis                    | 51.7        | 2.49                      | 0.80–7.71                   | 0.115                       |      |          |        |
| Transplant                         | 51.7        | 0.05                      | 0.00–2478.39                | 0.050                       |      |          |        |
| Low Income                         | 31.2        | 1.75                      | 1.24–2.47                   | 0.001                       | 1.74 | 1.24–2.45 | 0.002 |

AIDS = acquired-immunodeficiency syndrome, COPD = chronic obstructive pulmonary disease, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, OS = overall survival.

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findings rather than mycobacteriology or a history of anti-TB treatment. Nevertheless, these reports all emphasize that inflammation may cause EGFR mutations.

Using a large number of lung cancer patients with confirmed history of pulmonary TB, the present analyses demonstrate that pulmonary TB has a different impact on EGFR mutation and outcomes of lung cancer in female and male patients, resulting in a higher incidence of TKI-sensitive EGFR mutation and better 1-year PFS in female patients. Unlike in a previous study,18 these findings imply that pulmonary TB may result in different carcinogenesis processes between different genders. Possible explanations come from several studies showing different lung cancer presentation between males and females in the carcinogenesis of smoking, incidence of mutation in K-ras, c-erbB-2, or EGFR, and mortality.37 The differences may be related to genetic difference, decreased DNA repair capacity in female patients, and hormones.38,39 Women have been shown to have a greater risk of contracting tobacco-induced lung cancer for their lack of DNA repair ability compared with men.40 Nonetheless, estrogen simulates angiogenesis and increased angiogenesis is associated with tumor metastatic potential in lung cancer.41

TB also presents as different inflammations between male and female patients.32,42 Studies show that estrogen appears to act in synergy with interferon-γ to impair mycobacterial growth in mice by regulating interferon-γ promoter.44,45 It can be hypothesized that because of the lack of DNA repairing ability and estrogen-enhanced inflammation and angiogenesis, women are prone to more damages from inflammation that is induced by Mycobacterium tuberculosis, leading to a higher incidence of EGFR mutation. However, the detailed pathophysiology remains to be studied.

Apart from the association with EGFR mutation,5 tobacco smoking increases susceptibility to TB and is associated with treatment failure of TB.36,47 Since a history of smoking and other environmental factors such as exposure to biofuels are not available in the NHIRD of Taiwan, it is possible that some of the effect of pulmonary TB on EGFR mutation observed in present study is through the effect of those toxic substances. However, results of the sensitivity analysis focusing on lung cancer patients without COPD, malignancies other than lung cancer, and low income reveal an even greater impact of pulmonary TB history on EGFR-TKI response and 1-year PFS in the predominantly nonsmoking population. These findings suggest that the different effects of pulmonary TB on lung cancer patients with different genders are unlikely to be explained by smoking.

The results are compatible with findings of the IPASS and PIONEER studies, as well as other reports,2,4,5,48 showing that female gender and nonsmoking status are associated with better response to EGFR-TKIs, which, in turn, is associated with better OS. These findings also imply that the NHIRD of Taiwan can be a useful resource material for studying the long-term impact of pulmonary TB on the carcinogenesis and outcome of lung cancer.

This study has some limitations. First, results of molecular testing for the EGFR gene mutation are not available in this cohort. Although approval of EGFR-TKI use for >90 days require reaudit based on therapeutic response, using prescription duration of TKI >90 days as the surrogate of sensitive EGFR gene mutation may still have some bias. Second, even with similar findings in sensitivity analysis, the results of the present analyses may still be confounded by smoking. Third, the cohort may include some patients with squamous cell lung cancer, because erlotinib has a third-line indication in these patients in Taiwan. However, the number is limited because <40% of the study patients receive erlotinib and the most common cell type of lung cancer in Taiwan is adenocarcinoma, especially among female patients.49 In addition, few patients with squamous cell lung cancer can tolerate previous chemotherapy and go on third-line therapy.50

CONCLUSION

This study demonstrates that pulmonary TB has a gender-dependent impact, with better EGFR-TKI response and 1-year PFS in female, but worse in male patients. These results are different from those of the previous reports. The carcinogenesis and inflammation of TB may be different between male and female patients with lung cancer, but further large clinical trials are warranted to provide more evidence.

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