Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Non–Small-Cell Lung Cancer Patients with Leptomeningeal Carcinomatosis

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Background: Leptomeningeal carcinomatosis (LC) is a detrimental complication of patients with non–small-cell lung cancer (NSCLC). The effect of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) on the clinical outcome of these patients, particularly those with *EGFR* mutations, has not been studied yet.

Methods: We searched the database for lung cancer patients diagnosed from 2003 to 2010 in one Asian medical center. NSCLC patients who also had LC diagnosed by either cytology or brain neuroimaging studies were identified. The treatments and clinical outcomes were reviewed.

Results: Of 5526 lung cancer patients, we identified 212 (3.8%) NSCLC patients with LC. Most patients (88.7%) had adenocarcinoma histology, and 129 (60.9%) patients had been treated with at least one regimen of EGFR TKI before the diagnosis of LC. One hundred and twenty-four (58.5%) patients were treated with EGFR TKI, and 128 (60.4%) patients were treated with whole-brain radiation therapy (WBRT) after the diagnosis of LC. The median overall survival was 4.5 months (95% confidence interval, 3.5–7.3). Multivariate analysis suggested that EGFR TKI therapy, WBRT, and cytotoxic chemotherapy were independent predictors for longer survival. Mutational status of *EGFR* was evaluated in 101 patients, and 75 mutations (74.3%) were detected. Among the 75 patients with *EGFR* mutations, EGFR TKI therapy and cytotoxic chemotherapy after diagnosis of LC remained the independent factors predictive of extended survival in the multivariate analysis.

Conclusions: Treatment of LC with EGFR TKI, cytotoxic chemotherapy, or WBRT in selected patients is associated with prolong survival period. These treatment options, especially EGFR TKIs, should be studied in patients with *EGFR* mutation-positive NSCLC and LC.

Key Words: Epidermal growth factor receptor tyrosine kinase inhibitor, Leptomeningeal carcinomatosis, Non–small-cell lung cancer, Prognosis, Whole-brain radiation therapy.

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Leptomeningeal carcinomatosis (LC) in patients with non–small-cell lung cancer (NSCLC) is not uncommon.[1] A previous report from our hospital revealed that the incidence of LC proven by cytology was 0.7% in all lung cancer patients (including those with small-cell lung cancer) from 1992 to 2002.[2] However, in our daily practice, most patients are diagnosed with LC through radiologic diagnosis, particularly magnetic resonance imaging (MRI), correlated to clinical symptoms such as headache and signs of increased intracranial pressure. As a consequence, the incidence is higher than previously reported. Given the improvement of systemic therapy for extracranial lesions of metastatic NSCLC, patients now live long enough to develop LC.[3] Whole-brain radiation therapy (WBRT) and intrathecal chemotherapy (ITC) were the only treatment choice before the emergence of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs).[4]

The development of EGFR TKIs, including gefitinib and erlotinib, has changed the treatment of patients with NSCLC in the past 10 years.[5–7] Patients whose tumors harbor activating *EGFR* mutations, such as deletions in exon 19 and exon 21 L858R mutation, respond more frequently to EGFR TKI therapy.[5,8–10] *EGFR* mutation status has been a predictor of improved survival in NSCLC patients with brain metastases, but its role in patients with LC is not clear.[11] Some authors have reported that EGFR TKIs were effective in treating LC in patients with *EGFR* mutations.[12–14] In several retrospective studies, EGFR TKI therapy for LC was found to prolong survival, but the impact of *EGFR* mutations was not clear because of the small number of patients who underwent EGFR gene testing.[15–20] Gefitinib and erlotinib were available

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commercially in Taiwan in 2003 and 2006, respectively, to treat metastatic lung cancer. In this study, we calculate the incidence of LC diagnosed by radiology and/or cytology/histology in the era of EGFR TKI therapy. We also analyze the survival of patients with LC who underwent various local or systemic treatments.

MATERIALS AND METHODS

We screened patients diagnosed with lung cancer at National Taiwan University Hospital from January 2003 to December 2010 by linking data from two institutional databases: the Cancer Registry and the Medical Coding Specialist Section of the Medical Information Management Office at National Taiwan University Hospital, Taipei, Taiwan. Patients with cytologically or histologically diagnosed NSCLC and LC diagnosed by either cerebrospinal fluid (CSF) cytology or neuroimaging were identified. Regarding neuroimaging, LC was defined as the presence of multifocal enhancing subarachnoid nodules on gadolinium-enhanced brain MRI or contrast-enhanced computed tomography (CT).

Medical records of these patients were reviewed. We evaluated the demographic data, histology type, *EGFR* mutation status, treatments before diagnosis of LC (including EGFR TKIs, WBRT, and surgical resection of preexisting brain metastases), initial presentation of LC, concurrent brain metastases status on diagnosis of LC, and the time from diagnosis of metastatic NSCLC by cytology/histology to the diagnosis of LC. Treatments after diagnosis of LC were recorded, including cytotoxic chemotherapy, EGFR TKIs, ITC, Ommaya reservoir implantation, and ventriculoperitoneal (VP) shunt operation. All these treatments were at the discretion of treating physicians. The protocol of this study was approved by the Institutional Review Board of National Taiwan University Hospital.

Statistical Analysis

Overall survival (OS) time was determined from the date of diagnosis of LC (date of CSF cytology or neuroimaging examination) to the date of death or last follow-up. Patients who were discharged against medical advice with the intention to die at home according to Chinese custom in the final stage of the dying process were recorded as a death event. Data were analyzed as a censor if a patient was unavailable to follow-up or survived beyond the final date of medical record access (December 31, 2011).

The OS was estimated by the Kaplan–Meier method, and the differences between the study groups were compared by the log-rank test. Cox's proportional hazard model was used to estimate the univariate or adjusted hazard ratios and associated 95% confidence intervals (CI) to detect differences of OS. Multivariate analyses were performed by using the Cox's proportional hazard model, adjusted for gender, age, smoking status, and previous EGFR TKI therapy status of patients. Subgroup analyses focused on (1) patients with *EGFR* mutations and (2) EGFR TKI–pretreated patients who received another EGFR TKI therapy for LC or rechallenge of the previous EGFR TKI for LC with an EGFR TKI free interval of at least 6 months. Two-sided p values less than or equal to 0.05 were considered statistically significant. All analyses were performed by SAS statistics software, Version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Of the total of 5526 lung cancer patients screened, 212 (3.8%) patients with NSCLC and LC were identified. The median patient age was 56 years (range, 29–87 yr), 127 (59.9%) were female, 155 (73.1%) were never smokers, and 188 (88.7%) had adenocarcinoma histology. One hundred and twenty-nine (60.9%) patients had undergone EGFR TKI therapy before the diagnosis of LC. Most patients (47.6%) were diagnosed with LC by MRI and 19 (9.0%) patients were diagnosed with LC by a positive CSF cytology study (Table 1). The median time from diagnosis of metastatic disease to diagnosis of LC was 10.7 months (range, −1.5 to 55.5), and 48 (22.6%) patients had LC at initial diagnosis of metastatic NSCLC. Sixty-five (30.7%) patients had brain metastases on diagnosis of LC (Table 2). The most common symptoms on diagnosis were headache (49.0%), nausea/vomiting (41.5%), dizziness (24.1%), conscious change (21.7%), neurological deficit (17.9%), unsteady gait (14.2%), and seizure (8.0%). Fifteen (7.1%) patients were asymptomatic on diagnosis of LC.

Regarding local treatment for LC, 128 (60.4%) patients underwent WBRT, 23 (11.8%) patients underwent ITC, 31 (14.6%) patients underwent VP shunt operation, and 22 (10.4%) patients underwent Ommaya reservoir implantation. Regarding systemic therapy, 124 (58.5%) patients underwent EGFR TKI therapy, 22 (10.4%) patients underwent platinum-based cytotoxic chemotherapy, and 56 (26.4%) patients underwent nonplatinum-based cytotoxic chemotherapy after LC diagnosis (Table 2).

A total of 142 patients died, and 10 patients were still alive at the cut-off date. The median follow-up time was 2.5 months (range, 0–34.3), and the median survival was 4.5 months (95% CI, 3.5–7.3; Fig. 1). The median survival of different diagnostic modalities among CT, MRI, and CSF cytology were 6.5, 3.7, and 4.3 months, respectively ($p = 0.268$). Regarding systemic therapy, patients who received EGFR TKI therapy after LC diagnosis had longer OS than patients who did not (median 9.5 versus 1.7 months, $p < 0.001$; Fig. 2*A*). Patients who underwent cytotoxic chemotherapy also had longer OS (median, 10.2 versus 2.8 months, $p < 0.001$; Fig. 2*B*). As for local therapy, patients who underwent WBRT for LC survived longer (median, 8.4 versus 1.8 months, $p < 0.001$; Fig. 2*C*), but patients who underwent ITC (Fig. 2*D*), VP shunt operation, and Ommaya reservoir implantation did not. In a multivariate analysis adjusted for gender, age (≥70 or <70), smoking status, EGFR TKI naive or EGFR TKI pretreated, VP shunt operation, Ommaya reservoir implantation, EGFR TKI therapy after LC diagnosis, cytotoxic chemotherapy, and WBRT remained predictors of prolonged survival (Table 3).

One hundred and one patients had known *EGFR* mutation status, and 75 (74.3%) had *EGFR* mutations (common activating mutations of deletions in exon 19 and exon 21 L858R mutation were detected in 68 patients). Among

