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Original Article

Outcomes of research biopsies in clinical trials of *EGFR* mutation-positive non-small cell lung cancer patients pretreated with EGFR-tyrosine kinase inhibitors

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Background/purpose: Research biopsies (RBs) are crucial for developing novel molecular targeted agents. However, the safety and diagnostic yields of RBs have not been investigated in *EGFR* mutation-positive non-small cell lung cancer (NSCLC) patients pretreated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).
Methods: We searched the medical records of NSCLC patients who participated in lung cancer clinical trials and underwent mandatory RBs between 2012 and 2014 at our institution. Only patients with *EGFR* mutation-positive NSCLC pretreated with at least 1 EGFR-TKI were enrolled.
Results: Of 140 enrolled patients, 73 (52.1%) and 59 (42.1%) had exon 19 deletions and exon 21 L858R mutation, respectively. Before RBs, 108 (77.1%), 83 (59.3%), and 36 (25.7%) patients had

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Research biopsies

been treated with gefitinib, erlotinib, and afatinib, respectively. Computed tomography-guided percutaneous core needle biopsy was the most frequently used modality among 181 RBs performed (50.8%), followed by ultrasonography-guided (32.0%) and endoscopic RBs (16.0%). The most common RB sites were the lung (69.6%), pleura (8.8%), and liver (6.1%). Pathologic examinations revealed malignant cells in most RB specimens (72.9%). Complications due to RBs included pneumothorax (11.6%), bleeding (6.1%), and infection (1.1%). Only 1 patient required chest tube placement for pneumothorax, and 2 patients underwent endotracheal intubation because of bleeding.

Conclusions: RBs in this patient population were generally safe. Pneumothorax was the most frequent complication; bleeding, while infrequent, increased the risk of severe events. The diagnostic yields and complications of any particular modality should therefore be discussed with prospective clinical trial participants.

Introduction

In the era of personalized/precise anti-cancer therapy, physicians identify patients whose tumors harbor driver mutations in order to select appropriate treatments. For example, in patients with non-small cell lung cancer (NSCLC), *EGFR* mutation status (especially exon 19 deletions and exon 21 L858R mutation) is a good predictor of tumor response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).[1–3] The current standard of care is to select patients with activating *EGFR* mutations to undergo first-line EGFR-TKI monotherapy, such as gefitinib, erlotinib, or afatinib.[4–7] This prolongs progression-free survival compared to platinum-based doublet chemotherapy; overall survival is even prolonged in patients with exon 19 deletions who undergo first-line afatinib monotherapy compared to cisplatin plus pemetrexed or gemcitabine chemotherapy.[8] However, acquired resistance inevitably develops after a period of responsiveness. Common mechanisms of acquired resistance to EGFR-TKI therapy include *EGFR* exon 20 T790M mutation and *MET* amplification[9–12]; physicians identify these factors by performing tumor biopsies upon disease progression. Novel therapeutic agents are designed to overcome these common resistance mechanisms; for example, third-generation EGFR-TKIs and MET inhibitors can overcome *EGFR* T790M mutation and *MET* amplification, respectively.[13,14] However, it is mandatory to obtain research biopsies (RBs) to identify patient populations eligible to enroll in clinical trials of novel targeted therapies.

RBs have been controversial because of ethical considerations, safety, patient attitudes, feasibility, and other factors.[15–20] However, in recent trials such as the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) study conducted in the United States (in which patients with heavily pretreated advanced NSCLC prospectively underwent lung tumor re-biopsy to guide subsequent treatment based on identified molecular biomarkers), the complication rates of lung RBs were very low. Pneumothorax occurred in 11.5% of 139 patients; a single grade 3 event also occurred.[21] *EGFR* mutations were detected in only 15% of patients in that study, only 45% of whom had been treated with erlotinib. These results suggested that RBs may not be as risky as previously assumed. Therefore, we sought to determine the safety and diagnostic yield of RBs in *EGFR* mutation-positive NSCLC patients pretreated with advanced EGFR-TKI at our medical center.

Materials and methods

Patients

We reviewed medical records of patients aged ≥20 years with advanced *EGFR* mutation-positive NSCLC pretreated with EGFR-TKIs who participated in therapeutic clinical trials and underwent RBs between January 2012 and December 2014. The patient list was obtained from the Thoracic Oncology Multidisciplinary Team at National Taiwan University Hospital.

Data collection

We collected clinical data, including age, sex, tobacco use history, histological NSCLC type, *EGFR* mutation type, and treatments prior to participation in clinical trials and RBs. RB details recorded included the biopsy site, modality, and complications; results of pathologic exams and molecular biomarker tests; numbers of RBs undergone, and the clinical trials joined based on RB results. The protocol of this study was approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH-REC No.201412023RINC).

Statistical analyses

Patient characteristics, RB features, and outcomes were summarized by using descriptive statistics. Continuously scaled measures were summarized with descriptive statistical measures. Contingency tables were used to describe categorical data. The 95% confidence intervals of the risks of biopsy failure and complications were estimated based on binomial distributions. Fisher's exact test was used to examine the association between 2 categorical variables. A p-value <0.05 denoted statistical significance.

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