Editorial

Future prospects of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and surgery for non-small cell lung cancer

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Comment on: Du W, Zhao Y, Xuan Y, *et al.* Different efficacy in the non-small cell lung cancer patient with bilateral synchronous lesions treated with neoadjuvant gefitinib therapy: a case report. J Thorac Dis 2020;12:1582-7.

Song Y, Jia Z, Wang Y, *et al.* Potential treatment strategy for the rare osimertinib resistant mutation EGFR L718Q. J Thorac Dis 2020;12:2771-80.

Zheng Y, Zhou M, Arulananda S, *et al.* Management of non-small cell lung cancer with resistance to epidermal growth factor receptor tyrosine kinase inhibitor: case discussion. J Thorac Dis 2020;12:159-64.

Dai J, Greiffenstein P, Petrella F, *et al.* Treatment of a lung lobectomy patient with severe post-surgical infection in the anterior thoracic wall by multiple debridement and drainage procedures: a case report. J Thorac Dis 2020;12:7481-7.

Wang G, Lin Y, Zheng L, *et al.* A new method for accurately localizing and resecting pulmonary nodules. J Thorac Dis 2020;12:4973-84.

Jia Z, Wang Y, Cao L, *et al.* First-line treatment selection with organoids of an EGFRm + TP53m stage IA1 patient with early metastatic recurrence after radical surgery and follow-up. J Thorac Dis 2020;12:3764-73.

Zang J, Horinouchi H, Hanaoka J, *et al.* The role of salvage surgery in the treatment of a gefitinib-resistant non-small cell lung cancer patient: a case report. J Thorac Dis 2021;13:4554-9.

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Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have improved the prognosis of patients with non-small cell lung cancers (NSCLCs). Genetic testing by next-generation sequencing (NGS) has been used in multiple companion diagnoses or cancer genome profiling. This advance in genetic testing yielded new insights into the treatment of patients with NSCLC with mutations resistant to EGFR-TKIs. Recent studies have also reported the efficacy of EGFR-TKIs in the perioperative period. In this issue, we will briefly summarize new findings on adjuvant and neoadjuvant EGFR-TKIs and treatment for resistance to EGFR-TKIs. Subsequently, we will introduce seven papers on these topics.

A randomized controlled trial of osimertinib as adjuvant therapy (ADAURA study) showed that disease-free survival (DFS) in the osimertinib arm was significantly prolonged in patients with stage IB to IIIA *EGFR* mutation-positive NSCLC (1,2). Currently, a NeoADAURA study (ClinicalTrials.gov Identifier: NCT04351555, JapicCTI-205325) using osimertinib as neoadjuvant therapy is ongoing.

In many patients with *EGFR*-mutated advanced NSCLC, EGFR-TKIs as first-line therapy resulted in the acquisition of resistance within 1 year. In 50–60% of resistant cases, there was a T790M mutation in the exon 20 region of the *EGFR* gene (3). In a phase III AURA3 study comparing osimertinib with platinum-based chemotherapy in T790M mutation-positive NSCLC patients, osimertinib significantly prolonged progression-free survival (PFS) (median PFS; 10.1 *vs.* 4.4 months, hazard rate =0.30) (4). Furthermore, in a phase III FLAURA study comparing osimertinib with gefitinib or erlotinib as a first-line treatment for locally advanced *EGFR* mutation-positive NSCLC, PFS, and overall survival (OS) with osimertinib were significantly prolonged, and its toxicity was significantly reduced (5). Osimertinib was also effective

in cases of brain metastasis (6). Therefore, osimertinib is a promising option for the first-line treatment of *EGFR* mutation-positive NSCLC.

Even in patients treated with osimertinib for T790M mutation-positive NSCLC, resistance to osimertinib was reported to develop within 10 months (4). This acquired resistance includes C797S mutation, the activation of alternative pathways or downstream targets and histological transformation (3). In the future, the mechanism of resistance to osimertinib as a first-line treatment should be actively re-examined to elucidate it.

Du *et al.* reported a case in which NSCLC patients with *EGFR* mutations were safely treated with gefitinib before left lower lobectomy and mediastinal lymphadenectomy. Dai *et al.* reported a case in which patients suffered from severe postsurgical infection after lung lobectomy and recovered by multiple debridement and drainage procedures. Wang *et al.* introduced a novel surgical method for accurately localizing and resecting pulmonary nodules by injecting indocyanine green (ICG) under the guidance of an electromagnetic navigation bronchoscope. Zang *et al.* discussed the efficacy of salvage surgery after EGFR-TKI resistance. Jia *et al.* introduced first-line treatment selection by using organoids of an *EGFR*-mutated and *TP53*-mutated stage Ia1 patient with early metastatic recurrence after radical surgery and follow-up. Zheng *et al.* discussed therapeutic strategies for acquired resistance after gefitinib treatment. Song *et al.* reported a case of the rare osimertinib-resistant L718Q mutation. Although further studies are needed, we hope that these reports will help readers in their daily practice.

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