Editorial

Neoadjuvant gefitinib therapy: a potential standard therapy for non-small cell lung cancer

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Recently, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) have emerged as standard first-line therapies for EGFR mutant advanced non-small cell lung cancer (NSCLC) (1). Gefitinib was introduced as a first-generation EGFR-TKI in 2002, and subsequently, several additional EGFR-TKIs have been developed, including erlotinib (first generation), afatinib and dacomitinib (second generation), and osimertinib (third generation). Gefitinib has been shown to have dramatic efficacy in more than 70% of cases of advanced NSCLC with *EGFR* gene mutations. Despite these high response rates in *EGFR* mutant tumors, the median time to progression is approximately 1 year (2). However, osimertinib showed efficacy superior to that of gefitinib or erlotinib as a first-line treatment for *EGFR* mutation-positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events in FLAURA clinical trials (3). Moreover, the ARCHER 1050 trial (dacomitinib versus gefitinib) demonstrated that the investigational EGFR inhibitor dacomitinib exhibited a superior median progression-free survival in patients with previously untreated EGFR mutation-positive advanced NSCLC (4). Thus, the applications of gefitinib may be somewhat limited. By contrast, neoadjuvant targeted therapy has been applied as a multidisciplinary treatment for advanced NSCLC, and gefitinib may have an essential role in neoadjuvant therapy. In fact, some patients with inoperable systemic NSCLC exhibit a down staging of their cancer to operable disease status after gefitinib treatment (5).

An article by Du *et al.* reported the effectiveness of neoadjuvant gefitinib therapy in a single case of bilateral synchronous stage I lung adenocarcinoma. First, we would like to ask the authors about the selection of the treatment strategy used in this case. The decision regarding treatment differs depending on whether the clinical diagnosis is stage IV primary or stage I double primary lung cancer. We suspect that the authors diagnosed the tumor as left primary lung adenocarcinoma with contralateral pulmonary metastasis, which would explain why computed tomography-guided percutaneous needle biopsy was performed only for the left lung. Gefitinib is typically taken for 8 weeks in patients with *EGFR*-mutated left lung adenocarcinoma. Because analysis of EGFR-TKI treatment demonstrated partial response in the left lung adenocarcinoma and stable disease in the right lung tumor, the results implied that this case may have developed originally as synchronous multiple lung cancers. As a result, before initial treatment, both the right and left lung tumors should be biopsied. Furthermore, we would like to ask the authors if limited surgery, including segmentectomy, was considered to preserve respiratory function after the patient received EGFR-TKI therapy for 8 weeks.

Accordingly, the main subject of this report could be the neoadjuvant application of EGFR-TKIs. Because there are few reports on this topic, we think it would be worthy for publication. Based on current guidelines, neoadjuvant EGFR-TKIs are not recommended for the treatment of lung cancer; however, in the near future, a clinical study of patients with stage III or IV EGFR-mutated NSCLC should be performed in order to facilitate

the establishment of treatments to cure patients who have unresectable tumor. In general, neoadjuvant chemotherapy may cause several changes in the histology of primary tumors, including fibrosis and adhesion of connective tissue, which could complicate surgical interventions. In the case report in question, however, there were no adverse effects on the operation. We think these are important findings demonstrating lack of additional hydrothorax, tissue adherence and bleeding tendency. Moreover, gefitinib was shown to be a safe, feasible, and well-tolerated neoadjuvant therapy option. However, because gefitinib can cause interstitial pneumonia as a side effect, adaptation to neoadjuvant therapy should be carefully considered, and further accumulation of cases is necessary.

Neoadjuvant and adjuvant EGFR-TKI therapies have also attracted attention in the treatment of lung cancer. In a review paper, Nagasaka *et al.* stated that EGFR-TKI adjuvant therapy for resectable NSCLC could improve progression- free survival but may not translate into improved overall survival; thus, adjuvant targeted therapy remains controversial (6). In the ADAURA clinical trial, the efficacy and safety of osimertinib as an adjuvant therapy was studied, and the results showed that disease-free survival was significantly improved, whereas overall survival was not (7). Notably, although the efficacy of neoadjuvant EGFR-TKI therapy is still unclear, this treatment could improve survival outcomes in resectable NSCLC. Although neoadjuvant therapy may delay surgery and lead to a risk of disease progression, a meta-analysis demonstrated that pre-operative chemotherapy could improve overall survival (8). Considering the high response rates of EGFR-TKIs, we expect that EGFR-TKIs may show efficacy as neoadjuvant therapies. Lv *et al.* reported that neoadjuvant EGFR-TKI therapy yielded significantly higher response rates than chemotherapy and that postoperative complications, operation time, drainage volume, and postoperative hospital length of stay were comparable in patients with stage II–IIIA NSCLC (9). Additionally, a systematic review of neoadjuvant EGFR-TKI therapy concluded the therapy may provide a feasible treatment modality for patients with resectable or potentially resectable *EGFR*-mutant NSCLC, with satisfactory surgical outcomes and low toxicity (10).

In 2009, the IPASS study established the superiority of gefitinib over chemotherapy for advanced NSCLC with *EGFR* mutations (2). Despite the initial high response rates, patients on EGFR TKIs will inevitably become resistant to treatment. The most common mechanism of acquired resistance is T790M mutation, accounting for 50–60% of secondary resistance to primary EGFR-TKI therapy. This led to the development of osimertinib. Osimertinib is an irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and *EGFR* T790M resistance mutations, with lower activity against wild-type EGFR. In the FLAURA study, osimertinib had been shown to lead to better progression-free survival than first-generation EGFR-TKIs in the first-line setting; therefore, we suggest reconsidering the choice of gefitinib for *EGFR*-mutant NSCLC (3). Although the opportunity to use gefitinib for the treatment of advanced lung cancer is limited owing to acquired resistance, the high response rate may also play a role in pre-operative treatment, and resistance may not be an issue because of the short-term treatment. Thus, data from clinical trials using gefitinib compared with chemotherapy as a neoadjuvant therapy are essential.

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References

1. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v1-v27.
2. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
3. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
4. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:1454-66.
5. Hishida T, Nagai K, Mitsudomi T, et al. Salvage surgery for advanced non-small cell lung cancer after response to gefitinib. J Thorac Cardiovasc Surg 2010;140:e69-71.
6. Nagasaka M, Gadgeel SM. Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. Expert Rev Anticancer Ther 2018;18:63-70.
7. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
8. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.
9. Lv C, Ma Y, Feng Q, et al. Does neoadjuvant targeted therapy provide an opportunity for resectable EGFR-mutant lung cancer: a real-world retrospective study. J Thorac Dis 2020;12:5324-35.
10. Sun L, Guo YJ, Song J, et al. Neoadjuvant EGFR-TKI Therapy for EGFR-Mutant NSCLC: A Systematic Review and Pooled Analysis of Five Prospective Clinical Trials. Front Oncol 2020;10:586596.

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