



Neoadjuvant therapy for locally advanced non-small cell lung cancer: TKIs or immunotherapy?

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Our medical group recently published a study in the *Journal of Thoracic Disease* reporting the surgical experience in six patients with resectable epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) after gefitinib as neoadjuvant therapy (1). The publication of this manuscript has triggered a round of interest and discussion. As discussed in the article (1) and related editorials (2), our research was a retrospective study with limitations, consisting of six pooled cases for the purpose of revealing the procedure of neoadjuvant treatment. In this letter to the editor, we attempt to address several issues that were not revealed in the article due to the article type (1).

The article mainly retrospectively illustrated the procedure of radical resection after neoadjuvant targeted therapy (1). We described a typical case of radical surgical resection of residual disease after dramatic response to gefitinib in a patient with locally advanced lung adenocarcinoma harboring EGFR gene mutation to explore the efficacy of preoperative targeted neoadjuvant therapy. Five of the patients had preoperative stage IIIA of the disease, and one case had stage IIIB, according to the 7th edition of the clinical TNM (cTNM). The standard surgery included lobectomy and the mediastinal lymph node dissection. While preoperative gefitinib treatment made it possible to perform radical resection in these six cases, the surgery was performed and the suitable adjuvant therapy was arranged after the operation. Some other patients were excluded because radical resection was not permitted due to disease progression. One patient refused further surgical

intervention even when PR (partial response) was achieved by neoadjuvant targeted treatment. They continued to accept conservative therapy. The postoperative pathology of one of the patients who underwent surgery revealed small cell lung cancer mixed with adenocarcinoma, which led to the correct implementation of adjuvant therapy. The postoperative staging statistics are available in Table 1. The impact of treatment on the down-staging in these six cases was significant. Postoperative staging statistics show that one of the patients had stage IA of the disease, two cases had stage IIB, and three cases had stage IIIA. Although the results of the EMERGING-CTONG 1103 study and the primary objective were negative [The ORR for neoadjuvant treatment was 54.1% in the erlotinib arm compared with 34.3% in the control (CT) group (odds ratio, 2.26; 95% CI, 0.87–5.84; P=0.092)], and the median of PFS was significantly longer in patients treated with erlotinib (21.5 months) compared with the CT arm (11.4 months) (3). Our retrospective single-arm research also showed a long median of progression-free survival (PFS) than this multicenter-randomized-controlled trial study. Patients who received neoadjuvant therapy had a better physical situation before surgery than the patients who accepted neoadjuvant chemotherapy. Only the case of small cell lung cancer mixed with adenocarcinoma had bone metastasis with a PFS of 15 months, with no other recurrence happening. The patients were followed up for 12 to 30 months. Overall survival (OS) might not have been a good endpoint for this trial, because patients might have received back-line

therapy, such as chemotherapy/anti-VEGF drugs after disease progression. We still try to enroll more patients into this clinical trial. Complete follow-up data will also be collected, and the results of this study will be published in the corresponding article.

The immunotherapy (IO) is now suggested in patients with advanced NSCLC, both in the first-line of treatment and in later lines (4). The IMPOWER 150 study demonstrated that the addition of IO to the scheme of CT (carboplatin/paclitaxel) plus bevacizumab improved the PFS and the objective response rate (ORR) in EGFR-mutated patients (5). Forde *et al.* published a challenging study that evaluates the use of neoadjuvant nivolumab in a small cohort of patients (NCT02259621). Most of the patients were early-stage lung cancer, with all information about the status of EGFR unknown (6). IO in monotherapy or combined with CT is being evaluated in several clinical trials, such as KEYNOTE671, as a new induction treatment in patients with potentially resectable disease. These studies seem to suggest that IO has been firmly established in induction/neoadjuvant therapy for NSCLC. What we are concerned with is that there are still a number of issues to consider in the application of neoadjuvant IO, such as immune-related adverse events (irAEs), the possibility of disease hyperprogression in patients with EGFR mutations, the cost, and so on. The irAEs include endocrine disease, hepatitis, pneumonia, and neurologic syndromes (7). Postoperative pneumonia is difficult to distinguish from immune-related pneumonia. In fact, we have explored several cases of preoperative neoadjuvant IO for lung cancer in the monotherapy or combined with the CT method. Postoperative severe immune-related interstitial pneumonia and respiratory failure happened on postoperative day five in one case, which was difficult to differentiate from bacterial pneumonia at that time. In 2017, Kato *et al.* (8) also pointed out on CCR that EGFR mutation could initiate immune escape by up-regulating the expression of pd-1, pd-11, and CTLA-1. The results showed that 20% (2/10) of patients with EGFR mutations had hyperprogression, which increases the rate of progression 40 times. The cost of IO and irAE therapy is very high for patients. Patients with EGFR mutations are not good candidates for neoadjuvant IO therapy.

Neoadjuvant targeted and IO therapies are quite effective treatments for stage IIIA lung cancer, which is highly heterogeneous. Despite the results of the use of TKIs and IO in the first-line of treatment, new studies should be designed to evaluate neoadjuvant strategies. High-quality

prospective cohort studies remain highly valuable, and many unresolved issues require rigorous trial and complete data for verification.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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