



The superstars of precision medicine—EGFR inhibitors in adjuvant treatment of lung cancer

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We would like to thank the author of the editorial entitled “EGFR inhibitors in adjuvant treatment of lung cancer—the more specific, the better?” (1) for their interest and comments on our article “Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIa (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study” (2).

In the study of ADJUVANT/CTONG1104, EGFR-mutant non-small-cell lung cancer (NSCLC) was randomly assigned to either four cycles of adjuvant vinorelbine plus cisplatin or 24 months of gefitinib—an EGFR tyrosine kinase inhibitor. Disease-free survival (the primary endpoint) was significantly longer for patients assigned gefitinib than for those assigned cisplatin-based chemotherapy [median 28.7 months (95% CI, 24.9–32.5) *vs.* 18.0 months (13.6–22.3); hazard ratio (HR) =0.60; 95% CI, 0.42–0.87; *P*=0.0054]. 84 (79%) of 106 patients who received gefitinib received treatment for more than 1 year. At the same time, it was found that the safety and tolerability of the gefitinib group were acceptable. 12% of patients had grade 3–4 adverse events, mainly about liver function abnormalities. There was no interstitial pneumonia and no adverse events leading to death. The proportion of serious adverse events was less than chemotherapy. Therefore, it could be concluded that it was “the more specific, the better” for EGFR inhibitors in adjuvant treatment of lung cancer.

The sense of gefitinib in the adjuvant setting in clinical routine

The author of the editorial emphasized that it makes sense that the choice to select gefitinib in the adjuvant setting in clinical routine. Previous metastatic disease setting clinical trials showed that PFS was significantly longer in the gefitinib group than in the platinum-based treatment in EGFR-mutant NSCLC (3,4). The survival rate of lung cancer continues to be poor. Approximately half of the patients underwent resection would relapse locally or distantly. Chemotherapy has limitation of the improvement of survival rate (5). Therefore, it is necessary to explore more effective adjuvant treatment strategies continually.

The cost-effectiveness as well as adverse events of the EGFR TKIs

The author of the editorial put forward that the limitations should also be taken into account, especially the cost-effectiveness as well as adverse events of the TKIs.

Above all, the adjuvant treatment of EGFR-TKI is worth trying. The comparison of the adverse events between the gefitinib group as well as the vinorelbine plus cisplatin group in the study of ADJUVANT/CTONG1104 showed that dose reductions were reported by 12 (11%) of 106 patients who received gefitinib and 29 (33%) of 87 patients who

received vinorelbine plus cisplatin. Three (3%) patients who received gefitinib and 5 (6%) who received vinorelbine plus cisplatin discontinued treatment because of drug-related toxic effects. Meanwhile, 3% of the patients of the gefitinib group and 6% of the chemotherapy group could not receive treatments continuously. 13% of the patients of the gefitinib group were reported adverse events of grade 3–4, mainly due to abnormal liver function. While, up to 48% of patients in the chemotherapy group were reported adverse events grade 3 or 4 adverse events (2). The gefitinib group achieved longer DFS while maintained lower adverse events.

Although adverse events are unavoidable, in the study of ADJUVANT/CTONG1104, most patients were able to tolerate and continue to receive treatment after reasonable treatment. It is necessary to give education to patients and do close follow-up to intervene adverse events as soon as possible.

However, an adverse event of EGFR TKIs that is fortunately very rare, but often lethal, is interstitial lung disease. Prevention is important for interstitial lung disease. It is significantly to be alert when there are symptoms of the lungs, and use glucocorticoids if necessary.

Moreover, studies on the mechanisms of resistance are important to develop next-generation EGFR inhibitors to overcome resistance. For example, to overcome EGFR-sensitizing mutations or the T790M mutation, Osimertinib (AZD9291), a third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was born. Whether next-generation EGFR inhibitors will be better in the adjuvant therapy needs further study, such as the study of ADAURA, a phase III, double-blind, randomized study of osimertinib versus placebo in EGFR mutation-positive early-stage NSCLC after complete surgical resection (6).

Last but not least, the costs of TKIs do exist but are inevitable. The view of the author of the editorial was agreeable that when administering TKIs, it is mandatory to do close follow-up investigations of the patients for early detection of adverse events (7). In addition, in the future costs probably will decrease significantly as gefitinib patent protection ends soon and generic drugs are on their way to approval (1).

The most suitable treatment strategies come from “specific”

It was put by the author of the editorial that not all data about gefitinib is promising. As a conclusion of a phase II

open-label multicenter study of gefitinib in combination with irradiation followed by chemotherapy in patients with inoperable stage III non-small cell lung cancer, the benefit of gefitinib combined with radiotherapy could not be confirmed in the patient without EGFR mutation (8). However, the study of IPASS, a phase III, open-label study, drew a conclusion that gefitinib is superior to carboplatin–paclitaxel as an initial treatment for pulmonary adenocarcinoma among non-smokers or former light smokers in East Asia. The presence in the tumor of a mutation of the EGFR gene is a strong predictor of a better outcome with gefitinib (9). Moreover, in the study of ISEL, another phase III placebo-controlled study in advanced non-small cell lung cancer, EGFR gene copy number was a predictor of clinical benefit from gefitinib (10). The author of the editorial did not limit EGFR mutation status, hence, a negative result appeared. This is also a revelation that it is of significance that only taking “specific”—just as mentioned above, “the more specific, the better?”—into consideration, can the most suitable treatment strategies be chosen.

Overall, we are in agreement with the points raised by the author of the editorial. Indeed, the adjuvant treatment of EGFR-TKI in clinical routine is rapidly evolving, and the available scientific evidence increases swiftly. Therefore, we thank the author of the editorial for raising pertinent questions, for, in this field, every increase in knowledge is of significance. These will stimulate further research in the area of EGFR inhibitors in adjuvant treatment of lung cancer.

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Footnote

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

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