

Is epidermal growth factor receptor tyrosine kinase inhibitor in combination with cytotoxic chemotherapy a better treatment option for patients with *EGFR*-mutated non-small-cell lung cancer?

Kosuke Takahashi, Hiroshi Saito

Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Okazaki, Japan

Correspondence to: Kosuke Takahashi, MD. Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, 18 Kuriyado Kake-machi, Okazaki, Aichi 444-0011, Japan. Email: ktakahashi@acc-aichi.com.

Abstract: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) combined with cytotoxic chemotherapy achieved a high disease control rate and favorable progression-free survival (PFS) for *EGFR*-mutated non-small-cell lung cancer (NSCLC) patients. This combination therapy might circumvent *de novo* resistance to EGFR-TKI. Randomized phase III studies are required to confirm the survival benefit of this combination therapy in NSCLC patients. In addition, there are some other promising strategies including the combination of EGFR-TKI plus bevacizumab, third-generation EGFR-TKIs, and immune checkpoint inhibitors that remain a future challenge for lung cancer treatment.

Keywords: Combination drug therapy; epidermal growth factor receptor (EGFR); non-small-cell lung cancer (NSCLC)

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Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is demonstrated to have a dramatic response to non-small-cell lung cancer (NSCLC) harboring activating *EGFR* mutation (1-3). Therefore, it is considered as a standard treatment for patients with *EGFR*-mutated NSCLC. For further efficacy, the combination therapy with EGFR-TKI and cytotoxic agents has also been considered. However, recent studies on this combination therapy failed to demonstrate any further benefit for patients with NSCLC in comparison to chemotherapy (4-7). Two main reasons have been proposed for these failures. Firstly, the patients recruited in these studies were not selected by analyzing the *EGFR* mutation; thus, the efficacy of EGFR-TKI was diluted. Secondly, the preclinical studies indicated that the G1 phase arrest induced by EGFR-TKI may have interfered with the cell cycle-dependent cytotoxic chemotherapy (8). However, the second reason is not definitive. Two days of gefitinib treatment before paclitaxel was found to be more effective than the reverse treatment

pattern in tumor xenografts (9). In contrast, paclitaxel treatment followed by gefitinib produced a more anti-proliferative effect than the reverse pattern in NSCLC cell lines (10).

Sugawara *et al.* reported a randomized phase II study that evaluated the safety and efficacy of concurrent or sequential alternating regimen with gefitinib and carboplatin/pemetrexed in patients with *EGFR*-mutated NSCLC (11). The median progression-free survival (PFS) obtained in this study was 18.3 and 15.3 months for the concurrent and sequential alternating regimens, respectively. The PFS, especially in the concurrent group, is more favorable in comparison to the PFS in previous studies, which was 9.2 to 10.8 months with first-line gefitinib monotherapy for *EGFR*-mutated NSCLC patients (2,3). Clinically, *EGFR* mutant patients having disease progression after the first-line treatment of gefitinib or erlotinib, are administered with platinum-based chemotherapy. Since the median PFS of carboplatin and pemetrexed was 5.7 months (12),

the total PFS of the first-line gefitinib and the second-line carboplatin/pemetrexed treatment added up to about 15 to 16 months. Although the PFS of 18.3 months of the concurrent arm in the present study was longer than the added PFS, the difference was not substantial. A longer PFS benefit is expected from the concurrent regimen of the combination therapy that would outweigh the increased adverse events and cost of the treatment than the sum of PFS of each treatment given sequentially.

It should be noted that the disease control rate in this study is 100%, and the median overall survival (OS) time in the concurrent arm is 41.9 months. In general, approximately 10% of patients treated with first-line EGFR-TKI exhibit initial progression (2,3). Several mechanisms for the *de novo* resistance have been reported, and the early concurrent use of cytotoxic agents might be one of the countermeasures. OS must be interpreted with caution because of this being a randomized phase II study with immature survival data. The prolongation of the survival time is partly due to the long PFS of the first-line treatment and partly due to the long post-progression survival time. The efficacy of the second-line or third-line therapies as well as the improvement in the supportive care throughout the treatment might be partly responsible for the favorable post-progression survival time. Treating *EGFR*-mutated patients with EGFR-TKI has been shown to improve their OS. Updated median OS for the first-line gefitinib monotherapy in the NEJ002 and WJTOG3405 studies were 27.7 and 34.8 months, respectively (13,14). Moreover, median OS of the Japanese patients treated with the first-line afatinib was 46.9 months (15).

The most common grade 3 or greater adverse events in the study were neutropenia and thrombocytopenia. These hematological toxicities occurred most frequently in the concurrent group than in the sequential alternating group. The occurrence of non-hematologic toxicities like vomiting, appetite loss and diarrhea were also frequent in the concurrent group. Although almost half of the patients experienced grade 3 or greater adverse events, these events were still predictable and manageable. One of the greatest concerns in this combination therapy including EGFR-TKI is the increase of interstitial lung disease (ILD). However, in this study, only 5% of the total patients were observed to have ILD, which is comparable to that in EGFR-TKI monotherapy (2,3).

In addition to the combination of EGFR-TKI and cytotoxic chemotherapy, there are some other promising combination therapies including the combination of EGFR-

TKI plus bevacizumab, third-generation EGFR-TKI, and anti-programmed cell death-1 (PD-1) monoclonal antibodies.

Erlotinib combined with bevacizumab demonstrated a median PFS of 16.0 months, which was significantly better in comparison to erlotinib monotherapy (16). Almost all the patients (99%) in the erlotinib plus bevacizumab arm achieved disease control. While hypertension and proteinuria were commonly found in this combination therapy, serious adverse events also occurred at a similar frequency in both the groups. As this is a randomized phase II study, further evaluation is required to confirm the efficacy of such combination therapies.

The most common resistance mechanism after gefitinib or erlotinib is the acquisition of the second mutation in *EGFR*, which result in the substitution of threonine with methionine at the amino acid position 790 (T790M). AZD9291 is a selective third-generation inhibitor of both *EGFR* sensitizing and T790M resistance mutation. This inhibitor was reportedly administered to patients who had disease progression after being treated with EGFR-TKI (17,18). Its antitumor activity depended on the T790M status. The response rate was 61% and 21% and median PFS was 9.6 and 2.8 months in T790M-positive patients and T790M-negative patients, respectively. It was highly active in patients with NSCLC with T790M mutation who had disease progression during the initial EGFR-TKI therapy.

Nivolumab, a fully human anti-PD-1 immune checkpoint inhibitor antibody, was compared to docetaxel in patients with advanced non-squamous NSCLC after the failure of the platinum-based doublet chemotherapy (19). Nivolumab demonstrated superior OS of 12.2 months and improved response rate of 19.2%. Although the response rate was not remarkable, the median response duration of 17.1 months attracted more attention. This monoclonal antibody had durable responses in the limited subset of patients. Although high PD-L1 expression correlated with positive treatment outcomes, this association was not conclusive. Search for new reliable predictive markers is essential to spare non-responders from unnecessary toxicities and financial burden of the treatment.

In conclusion, EGFR-TKI plays an essential role in the treatment of *EGFR*-mutated NSCLC patients. Combination therapy of EGFR-TKI and cytotoxic chemotherapy is attractive in the light of favorable PFS and high disease control rate. As described above, with the development of new promising drugs, further prolongation of OS might be

achievable. The main challenge is how to combine the first- to third-generation EGFR-TKIs, cytotoxic chemotherapies, bevacizumab, and immune checkpoint inhibitors, either concurrently or sequentially, for the treatment of EGFR-mutated NSCLC patients.

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Footnote

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