

Clinical efficacy of EGFR-TKIs in combination with chemotherapy in patients with advanced non-small cell lung cancer harboring EGFR mutations

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Lung cancer, broadly divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), is the leading cause of cancer-related death in both the United States and China (1,2). The majority of new cases are advanced NSCLC at the time of diagnosis, and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are recommended to be the standard treatment option for advanced NSCLC patients harbouring activating *EGFR* mutation (3). Several randomized controlled trials that enrolled patients with EGFR-mutated NSCLC demonstrated that EGFR-TKI was superior to chemotherapy in terms of progression-free survival (PFS) and objective response rate (ORR) (4-7). However, concomitant administration of EGFR-TKIs standard chemotherapy is controversial.

Our previous meta-analysis showed EGFR-TKIs in combination with chemotherapy had a significant benefit on PFS [hazard ratio (HR) =0.80; 95% CI, 0.71–0.90; P<0.001] and ORR (RR =1.35; 95% CI, 1.14–1.59; P<0.001). However, the combined regimen had no significant impact on overall survival (OS) (HR =0.96; 95% CI, 0.90–1.03; P=0.25). Subgroup analysis showed significantly higher OS advantages in *EGFR* mutation positive patients (P=0.01) (8). Unfortunately, the EGFR-mutation status was only assessed in a few patients, and as such, further prospective clinical trials are needed for more substantial evidence to clarify this issue.

Recently, Cheng *et al.* (9) reported a double blind, randomized, placebo-controlled phase II study that compared first-line pemetrexed plus gefitinib (P+G) versus

gefitinib (G) alone in East Asian patients with EGFR-mutated advanced non-squamous (NS) NSCLC. This is the first randomized study to evaluate the efficacy of synchronous combination of pemetrexed and gefitinib in patients with advanced NSCLC harboring a sensitive *EGFR* mutation. The primary end point of this study was PFS. Secondary end points were time to progressive disease, OS, tumor response rates, duration of response, and safety. Of 232 patients enrolled, there were 191 assessable patients (126 P+G; 65 G). In this study, PFS was prolonged with P+G versus G (median, 15.8 *vs.* 10.9 months, respectively; adjusted HR =0.68; 95% CI, 0.48–0.96; one side P=0.014; two-sided P=0.029). Median time to progressive disease was also prolonged with P+G compared with G (median, 16.2 *vs.* 10.9 months, respectively; HR =0.66; 95% CI, 0.47–0.93; P=0.018). OS data were immature. The primary grade 3–5 toxicities were ALT/AST increased (22% for P+G *vs.* 11% for G) and neutrophil count decreased (5% for P+G *vs.* 2% for G). This study demonstrated concomitant administration EGFR-TKIs with standard chemotherapy is a viable first-line option for patients with EGFR-mutated NS NSCLC. Importantly, the study identified patients who can benefit the most from combination therapy and further emphasized the need to test the mutation status at the time of diagnosis. However, this study did not include non-Asian patients; further studies are needed to clarify the efficacy of pemetrexed in combination with gefitinib in non-Asian patients with advanced NSCLC harboring activating *EGFR* mutation.

In 2015, Yoshimura *et al.* (10) also analysed the

combination regimen of gefitinib and pemetrexed as first-line treatment in patients with advanced NSCLC harboring a sensitive *EGFR* mutation. This study enrolled 26 patients, and didn't set the control group. The ORR was 84.6%, disease control rate (DCR) was 96.2%, and the median PFS was 18.0 months. In addition, Yang *et al.* (11) study reported that first-line pemetrexed plus cisplatin (PC) followed by gefitinib maintenance therapy versus gefitinib monotherapy in East Asian never-smoker patients with locally advanced or metastatic NS-NSCLC. A total of 236 patients were randomly assigned, 118 to each arm (PC/G or G). *EGFR* mutation status was retrospectively determined for 76 patients, including 52 patients (68.4%) with *EGFR* mutation. This study showed that median OS was similar in the PC/G and G groups (median, 26.9 *vs.* 27.9 months). Subgroup analyses based on *EGFR* mutation status showed that median OS was 28.4 months with PC/G and 8.9 months with G in *EGFR* wild type patients. In contrast, median OS was longer with G group than with PC/G group in patients with harboring a sensitive *EGFR* mutation. However, a limitation of the study was that tumor *EGFR* mutation status could be determined for only a small proportion of patients. Therefore, this result should be interpreted with caution.

Two methods of drug delivery were adopted in the combination group, including concurrent and intercalated administration. For the first method, four large-scale phases III randomized controlled trials, including INTACT-1, INTACT-2, TALENT, and TRIBUTE, were performed to evaluate if chemotherapy combined with EGFR-TKIs synchronously as the first-line treatment for advanced NSCLC patients could improve survival (12-15). The results showed that chemotherapy combined with EGFR-TKIs synchronously did not confer a survival benefit to patients with advanced NSCLC. Concurrent administration may not be effective because of TKI-induced, G1-phase cell-cycle arrest (16). Another important reason is that the *EGFR*-mutation status was determined in a few patients enrolled in previous clinical trials. Cheng *et al.* study made up for the shortcomings of previous studies. For the second method, the FASTACT-2 trial showed the intercalated regimen improved the PFS and OS (17). When *EGFR*-TKI and chemotherapy are given in a sequentially intercalated way, thus achieving pharmacodynamic separation of the two agents, the inhibitory drug interaction could be avoided (18). It is still unanswered which administrating schedule will produce the best efficacy. Therefore, a head-to-head study is needed to define the best administrating schedule.

In conclusion, Cheng *et al.* study provides a basis for implementation of gefitinib in combination with pemetrexed in patients with advanced NSCLC harboring a sensitive *EGFR* mutation. Well-designed large-scale phases III randomized controlled trials are needed to confirm these findings.

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None.

Footnote

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

Comment on: Cheng Y, Murakami H, Yang PC, *et al.* Randomized Phase II Trial of Gefitinib With and Without Pemetrexed as First-Line Therapy in Patients With Advanced Nonsquamous Non-Small-Cell Lung Cancer With Activating Epidermal Growth Factor Receptor Mutations. *J Clin Oncol* 2016;34:3258-66.

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