Editorial

Gefitinib in combination with pemetrexed in patients with advanced non-small cell lung cancer harboring EGFR mutations: is there any difference in acquired resistance mechanism between gefitinib monotherapy and the combination treatment?

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Somatic mutations within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are the most reliable predictors of efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in patients with non-small cell lung cancer (NSCLC). In randomized phase III trials, EGFR-TKIs in patients with advanced EGFR mutant NSCLC were associated with longer progression-free survival (PFS) and higher radiographic response rates than the standard first-line platinum-based chemotherapy (1-7). Based on these results, three types of EGFR-TKIs, gefitinib, erlotinib and afatinib have been approved for treatment of advanced EGFR-mutant NSCLC as a first-line setting. Despite an initially marked response, almost all patients treated with EGFR-TKIs eventually acquire resistance to these drugs, with an average PFS of around 1 year. To improve these results, several combinations of EGFR-TKIs and other drugs, such as targeted drugs and chemotherapy, have been developed.

One of the candidates in combination with EGFR-TKIs is an antiangiogenic agent. The JO25567 trial is a randomized, open-label phase II study that compared the EGFR-TKI erlotinib monotherapy versus erlotinib plus bevacizumab, a monoclonal anti-vascular endothelial growth factor (VEGF) antibody, in patients with untreated EGFR-mutant advanced NSCLC. This study demonstrated a significant better PFS and tumor response for erlotinib plus bevacizumab compared with erlotinib monotherapy [median PFS of 16.0 *vs.* 9.7 months; hazard ratio (HR) =0.54, 95% confidence interval (CI): 0.36–0.79, P=0.0015; overall response rate (ORR) 69% *vs.* 64%] (8). Because of these favorable results, a randomized phase III study comparing erlotinib monotherapy and erlotinib plus bevacizumab is currently underway in Japan (UMIN000017069). Furthermore, another antiangiogenic agent, ramucirumab, a monoclonal antibody against anti-VEGF receptor 2, has been evaluated in combination with erlotinib in a global randomized phase III study (NCT02411448).

Another candidate is chemotherapy. Cheng *et al*. recently reported a multicenter, randomized, open-label, parallel-arm, phase II study comparing first-line pemetrexed plus gefitinib versus gefitinib monotherapy in untreated EGFR-mutant advanced NSCLC patients (9). Pemetrexed is one of the standard cytotoxic chemotherapy drugs for patients with locally advanced or metastatic non-squamous NSCLC. Preclinical and early clinical studies also indicate a potential synergy between pemetrexed and EGFR-TKIs (10-13). Based on these evidences, this clinical trial was conducted. The primary endpoint in this study was PFS. Of 232 patients enrolled, 195 were randomly assigned to pemetrexed plus gefitinib (P+G: n=129) or gefitinib monotherapy (G: n=66). Of these, 191 patients received at least 1 dose of the study drug. As per efficacy, there was a

statistically significant prolongation of PFS in the P+G arm (median PFS: 15.8 months; 95% CI: 12.6–18.3 months) compared with the G arm (median PFS of 15.8 *vs.* 10.9 months, adjusted HR =0.68, 95% CI: 0.48–0.96, one-sided P=0.014, two-sided P=0.029). Overall survival (OS) data is immature. Concerning safety, a significantly higher proportion of patients in the P+G arm compared with the G arm reported one or more possibly drug-related grade 3 or 4 treatment related adverse events (42% *vs.* 19%, P=0.001), reflecting the expected additional events for both study drugs. The most commonly reported grades 3–5 toxicities were alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase (ALT increased: 16% for P+G *vs.* 8% for G, and AST increased: 6% for P+G *vs.* 3% for G), which is consistent with the known safety profiles of both drugs. Despite the increase in toxicity with P+G, these toxicities were clinically manageable. This study demonstrated that EGFR-TKIs with pemetrexed are a new first-line option for patients with EGFR-mutated NSCLC.

There have been several clinical trials of combinations with EGFR-TKIs and chemotherapy in advanced NSCLC. Four previous phase III studies (INTACT-1, INTACT-2, TRIBUTE, and TALENT) that compared platinum doublet chemotherapy with or without EGFR-TKIs and were performed in patients with untreated advanced NSCLC regardless of their EGFR mutation status (14-17). These studies showed no additional survival benefit for the combination of chemotherapy and EGFR-TKIs. However, patients in these studies were not included accounting for the presence of EGFR mutation, which is the most reliable predictor of the efficacy of EGFR-TKIs. In fact, several phase II studies to evaluate the efficacy of chemotherapy/EGFR-TKIs combination in patients with advanced NSCLC harboring a sensitive EGFR mutation showed an encouraging PFS (around 18 months) and OS (32–48 months) (18-20). In addition, FASTACT-2, which is phase III trial comparing erlotinib intercalated with chemotherapy versus chemotherapy plus placebo in patients with advanced NSCLC, showed a significant benefit only in EGFR-mutant NSCLC (median PFS of 16.8 *vs.* 6.9 months; HR =0.25, 95% CI: 0.16–0.39, P<0.0001; median OS, of 31.4 *vs.* 20.6 months, HR =0.48, 95% CI: 0.27–0.84, P=0.0092). On the other hand, no difference was observed in the subgroup with EGFR wild-type NSCLC (PFS, median of 6.7 *vs.* 5.9 months, HR =0.97, 95% CI: 0.69–1.36, P=0.8467; OS, median of 14.9 *vs.* 12.2 months, HR =0.77, 95% CI: 0.53–1.11, P=0.1612) (21). Two phase III studies comparing gefitinib monotherapy with concurrent combination therapy of gefitinib and carboplatin plus pemetrexed (UMIN000006340), and comparing gefitinib monotherapy and gefitinib combined with inserted cisplatin plus pemetrexed (UMIN000020242) in patients with advanced NSCLC harboring EGFR mutation are ongoing in Japan.

Moreover, there have been no results concerning the difference in acquired resistance mechanisms between EGFR-TKI monotherapy and the combination treatment. Interestingly, the Cheng *et al*. study showed that the Kaplan-Meier curves of PFS in this study for the two arms overlapped for the first 7 to 8 months but diverged at later time points in favor of the P+G arm. This might mean that there were some differences in acquired resistance mechanisms between the P+G arm and G arm, although this study did not include the results of EGFR-TKIs resistance. Several acquired resistance mechanisms of EGFR-TKIs have been identified, including the emergence of the EGFR T790M mutation, MET amplification, transformation to small cell lung cancer, or development of PIK3CA and KRAS mutations (22-26), although there are only a few reports on the mechanism of the primary resistance to EGFR-TKIs (27-30). Of special note, the emergence of EGFR T790M mutation has been reported in approximately 50% of patients at the time of acquired resistance to EGFR-TKIs (31). Moreover, third-generation EGFR-TKIs like osimertinib, which is an irreversible, mutant-selective EGFR-TKIs developed to have potency against EGFR mutations such as the T790M mutation, were recently approved for the treatment of EGFR T790M mutation positive NSCLC based on the results of early clinical trials (32,33). A randomized, phase III trial assessed the efficacy and safety of osimertinib as a second-line treatment in more than 400 patients who were EGFR T790M mutant-positive and exhibited locally-advanced or metastatic NSCLC which progressed following first-line EGFR-TKIs therapy. This phase III trial demonstrated that osimertinib showed significant and meaningful improvements in PFS and ORR in these patients compared with standard platinum-doublet chemotherapy (34). Identification of EGFR T790M mutation after EGFR-TKIs failure has been an important requirement for selecting subsequent appropriate treatment that includes osimertinib. Therefore, understanding the difference in EGFR-TKIs acquired resistance mechanisms between EGFR-TKIs monotherapy and the combination treatment with both EGFR-TKIs and chemotherapy is important.

In conclusion, the Cheng *et al*. study showed that

patients with advanced EGFR mutant NSCLC obtain clinical benefit from the addition of pemetrexed to EGFR-TKIs as a first-line setting. However, understanding the difference in resistance mechanisms between G and G+P, which include the emergence of EGFR T790M mutation, is also important.

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