Editorial

Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harboring EGFR mutations (JO25567): an open-label, randomized, multicenter, phase II study

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The JO25567 study was a randomized phase II study to investigate the efficacy of the combination therapy consisted with erlotinib and bevacizumab for non-squamous non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) activating mutation (1). The study showed that the progression-free survival (PFS) of the combination therapy group was longer than that of the erlotinib monotherapy group. The median PFS were 16.0 months (95% CI, 13.9-18.1) *vs.* 9.7 months (95% CI, 5.7-11.1) respectively. The over-all survival (OS) data are immature, but this study suggested a remarkable efficacy of this combination chemotherapy.

Angiogenesis is essential for tumor growth, and a high microvessel density has been identified as a worse prognostic and a predictive factor of metastasis. Vascular endothelial growth factor (VEGF) was identified as the most potent and specific angiogenic mitogen for endothelial cells. VEGF expression is regulated by many cytokines and growth factors, for example interleukin-1, interleukin-6, transforming growth factor (TGF), and basic fibroblast growth factor, and so on. EGFR is expressed on vascular endothelial cells, which induce tube formation in response to EGF or TGF-alpha. Signaling through the EGFR axis also plays a role in the regulation of angiogenesis. At the cellular level, activation of EGFR by its ligands such as EGF or TGF-alpha results in increased VEGF expression (2). EGFR-tyrosine kinase inhibitors (EGFR-TKIs) inhibit tumor cell growth and blocks synthesis of angiogenic proteins by tumor cells, like VEGF and, TGF-alpha. In addition, VEGF production is upregulated by hypoxia via hypoxia-inducible factors (HIFs) in HIH3T3 cells transfected with mutant EGFR constructs. Hypoxia which is common in solid tumors then turns on the signal to initiate angiogenesis. Although the mechanism has not been clearly elucidated, it is suggested that EGFR is associated with enhanced signaling by phosphatidylinositol 3-kinase, which synergizes with hypoxia to regulate VEGF (3). Also, a recent study demonstrated a novel molecular pathway in which hypoxia promotes tumor growth by transcriptional activation of the Met proto oncogene. Through these some pathways, VEGF was regulated in tumors.

With regard to prognosis, the role of angiogenesis has been established in the progression of lung cancers. Results from a retrospective study in Japan showed that the serum concentrations of EGF, hepatocyte growth factor (HGF), and VEGF in patients with NSCLC who received EGFR-TKI were significantly higher among patients with progressive disease (PD) than among those with stable disease (SD) or partial response (PR) (4). Increasing HGF and VEGF concentrations were significantly associated with lesser tumor shrinkage, independent of the EGFR mutation status. Furthermore, the higher concentrations of HGF and VEGF were significantly associated with shorter PFS and OS. The study suggested that the serum concentration of VEGF might be an independent prognostic factor in NSCLC.

Excessive angiogenesis is also associated with resistance to EGFR-TKI. First-line treatment with an EGFR-TKI of

patients with advanced NSCLC harboring EGFR-activating has been shown to yield longer PFS periods than treatment with platinum-doublet chemotherapy. However, most patients develop resistance to EGFR-TKIs after the initial response. Several mechanisms associated with resistance to EGFR-TKIs have been identified: exon 20 T790M point mutation, Met gene amplification, translocation for small-cell lung cancer. Some preclinical studies to overcome the resistance have suggested that a combination of an EGFR-TKI and anti-VEGF therapy could enhance antitumor activity in NSCLC cells harboring an EGFR mutation, especially in cells that express high levels of VEGF. Several mechanisms of antitumor activity of the combination therapy have been found. Tumor blood vessels are structurally and functionally abnormal by angiogenesis. Because abnormal tumor vessels are hyperpermeable, the pressure gradient may be insufficient to ensure effective flow of drug from the vessel lumen to the tumor cells. Bevacizumab blocks angiogenesis by decreasing VEGF levels, and EGFR-TKI blocks synthesis of VEGF and TGF, they normalize tumor vessels transiently. The normalized vessels makes tumor more sensitive to chemotherapy, and improve tumor oxygenation and restore delivery of drug into tumor by decreasing interstitial fluid pressure. In addition, EGFR plays a role in the regulation of cell proliferation. Partial normalization of tumor vessels by bevacizumab causes proliferation of the tumor cells, which make them more sensitive to EGFR-TKI.

Bevacizumab is a monoclonal antibody that targets VEGF-A, and it has been an important adjunct in the treatment of colorectal cancer. In colorectal cancer, the possible efficacy of a combined therapy with cetuximab and bevacizumab was reported already in 2007. The BOND-2 study was a randomized phase II trial to investigate the feasibility of the combination therapy cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab in patients with irinotecan-refractory colorectal cancer (5). The results showed that response rates and time to tumor progression in both groups compared favorably with historical controls, and toxicities were as they would have been expected to be from the individual agents especially in the dual antibody treatment with irinotecan. In a molecular biological analysis of this trial, high intratumoral gene expression levels of EGFR, VEGFR2 which might signify a ligand-dependent tumor were associated with longer OS. Although the results of the BOND-2 trial cannot be used directly as evidence of efficacy of combination therapy with EGFR-TKI and anti-VEGF therapy in NSCLC harboring EGFR mutations, the results suggest that this combination might be able to overcome primary or acquired resistance to EGFR-TKIs. At this time, a phase I/II study of the combination therapy with carboplatin, pemetrexed, erlotinib and bevacizumab for NSCLC harboring EGFR mutations is ongoing. The results of this trial are expected shortly. In colorectal cancer, two large phase III trials investigating the safety and efficacy of combination therapies incorporating chemotherapy, bevacizumab, and EGFR-inhibitor have been reported. Both studies observed no additional clinical benefit of anti-EGFR antibody compared to chemotherapy with bevacizumab alone and increased toxicity. Thus, there is also a possibility that the phase I/II study of NSCLC may show no benefit and increasing toxicity.

Recently, third generation EGFR-TKIs have been developed. Some phase I studies of patients with NSCLC who had acquired resistance to EGFR-TKIs have shown that this new generation of EGFR-TKIs was more effective in patients who were positive for the T790M mutation than in those who were negative. Thus, the third generation EGFR-TKIs will be promising drugs for patients with the T790M mutation, but not for those without it. New strategies should be investigated for treating patients who are negative for the T790M mutation. The combination therapy with EGFR-TKI and bevacizumab may be a potential solution for this population.

The JO25567 study was the first to obtain clinical data that showed the efficacy of the combination therapy with bevacizumab and EGFR-TKI in first-line treatment of patients with NSCLC harboring an EGFR-activating mutation. The OS data are not shown, a larger randomized phase III trial will be required to establish the efficacy of this combination therapy.

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