Editorial Commentary

Prospects for the future of epidermal growth factor receptor-tyrosine kinase inhibitors in combination with bevacizumab

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Lung cancer is a major cause of cancer-related death. The main initial treatment for advanced and recurrent lung cancer is systemic chemotherapy. The survival rates for first line platinum-based chemotherapy, which is the cornerstone chemotherapy for non-small cell lung cancer (NSCLC), are poor (1). However, the survival rate of NSCLC, particularly adenocarcinoma, has recently improved with the development of strategies involving molecular-targeted therapies, angiogenesis inhibitors, and checkpoint inhibitors. The treatment strategy for NSCLC is evolving.

Since the approval of gefitinib, which was the first epidermal growth factor receptor (EGFR) inhibitor to reach the market, EGFR-tyrosine kinase inhibitors (TKIs) have displayed efficacy in the treatment in patients with mutated EGFR (2,3). The progression-free survival (PFS) of first- and second-generation EGFR-TKIs (e.g., gefitinib, erlotinib, afatinib) is approximately 1 year, and acquired resistance (AR) is mostly inevitable (4). Meanwhile, the third-generation EGFR-TKI osimertinib prolonged PFS to 18.9 months (5). Treatment with EGFR-TKIs has progressed rapidly in this decade. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), had prolonged PFS for NSCLC without squamous cell carcinoma in combination with platinum doublets (6). Recently, some clinical studies of EGFR-TKI treatment combined with bevacizumab were performed to improve prognosis for EGFR-positive NSCLC (7-10).

In patients with EGFR-mutated non-squamous NSCLC, erlotinib plus bevacizumab improved PFS compared with the effects of erlotinib alone in a phase III trial (NEJ026) conducted by Saito *et al.* (7). In the NEJ026 study, 228 patients with non-squamous NSCLC harboring common EGFR mutations were randomized to receive either oral erlotinib 150 mg per day plus intravenous bevacizumab 15 mg/kg once every 21 days or erlotinib 150 mg per day alone. In the interim analysis, the median PFS of patients in the erlotinib plus bevacizumab group was 16.9 months, compared with 13.3 months for patients in the erlotinib group [hazard ratio (HR) 0.606, 95% confidence interval (CI): 0.417–0.877; P=0.016). The objective response rates in the combination and monotherapy arms were 72% and 66% (P=0.31), respectively, and the disease control rates were 95% and 96% (P=0.52), respectively. All patients in the erlotinib plus bevacizumab group had a decrease in tumor size *vs.* baseline, although a few patients in the erlotinib group experienced such an increase. Subgroup analysis by EGFR genomic aberration type revealed that the median PFS was better in patients with the L858R mutation in the erlotinib plus bevacizumab group than in the erlotinib group (17.4 *vs.* 13.7 months, HR 0.57, 95% CI: 0.33–0.97). Conversely, no differences in survival were found between the erlotinib plus bevacizumab and erlotinib alone groups in patients with exon 19 deletion (16.6 *vs.* 12.4 months, HR 0.69, 95% CI: 0.41–1.16). In subgroup analyses by CNS metastasis and pleural effusion (PE), the HR for PFS was better the erlotinib plus bevacizumab

group than the erlotinib group, although these differences were not statistically significant (HR 0.78, 95% CI: 0.42–1.43 and HR 0.58, 95% CI: 0.34–1.02, respectively). Adverse events of grade 3 or worse were more common in the erlotinib plus bevacizumab group than in the erlotinib group (88% and 46%, respectively). The median duration of erlotinib administration was 405 days (range, 5–807 days) in the erlotinib plus bevacizumab group, *vs.* 364 days (range, 43–736 days) in the erlotinib group. The most commonly reported adverse events causing bevacizumab discontinuation were proteinuria [11 (33%) patients], hemorrhage [excluding pulmonary hemorrhage; 3 (9%) patients], and hepatic dysfunction [3 (9%) patients]. The most commonly reported adverse events resulting in erlotinib discontinuation were rash [8 (7%) patients in the erlotinib plus bevacizumab group and 8 (7%) patients in the erlotinib group].

To the best of our knowledge, NEJ026 is the first multicenter phase 3 study to compare the efficacy of bevacizumab plus an EGFR-TKI with an EGFR-TKI alone in patients with NSCLC. Regarding the EGFR genomic aberration type, some studies (11-13) reported better efficacy in patients with exon 19 deletion than in those carrying the L858R mutation. A greater number of samples may result in different results, but erlotinib plus bevacizumab may have better efficacy for patients with the L858R mutation than in those with exon 19 deletion. Regarding phase 2 trials, some studies assessed bevacizumab and EGFR-TKI combination treatment (5,8-10,14). Kitagawa *et al.* reported a phase 2 study (9) comparing gefitinib plus bevacizumab to single agent of gefitinib in patients with EGFR-positive NSCLC. This study concluded that PFS was worse in the gefitinib with bevacizumab group than in the gefitinib group (5.4 and 15.1 months, respectively); and hence, there was not able to proceed to a phase III trial. However, comparisons with other results could be difficult because this study was small (n=16). Hata *et al.* reported a phase 2 study (10) assessing afatinib plus bevacizumab after AR to EGFR-TKIs in patients with EGFR-mutant NSCLC. This study reported that afatinib plus bevacizumab was clinically effective and safe after AR to EGFR-TKIs, showing that it could be a therapeutic strategy option for patients carrying the T790M mutation. However, this was a single-arm study opposed to a controlled trial.

Osimertinib, a third-generation EGFR-TKI, was linked to better prognosis than platinum doublet chemotherapy in patients with EGFR T790M-mutated lung cancer in the phase III AURA3 trial (15). Moreover, osimertinib was determined to be the best TKI in terms of PFS based on the results of the FLAURA study (5). Currently, two phase I/II studies of osimertinib plus bevacizumab are ongoing (WJOG8715L, SPIRAL II) (8,16). WJOG8715 is a phase I/II study of osimertinib plus bevacizumab in patients with EGFR-mutated, T790M-positive cancer who acquired resistance on EGFR-TKIs, and SPIRAL II is a phase II trial of osimertinib plus bevacizumab in patients with non-therapy EGFR-mutated NSCLC and malignant PE and/or pericardial effusion. Both are single-arm studies. In the future, a controlled trial of osimertinib with bevacizumab *vs.* osimertinib alone in patients with EGFR-mutated cancer could lead to improved outcomes.

Regarding CNS metastasis and PE, the NEJ026 study (7) did not reveal a significant benefit of erlotinib plus bevacizumab. However, erlotinib could be more effective for the treatment for CNS metastases than gefitinib or afatinib (17,18). *In vivo* data indicated that anti-VEGF treatments could be useful for controlling malignant PE (19). Moreover, we previously reported the effect of erlotinib with bevacizumab to brain metastases in patients with NSCLC (20). In NEJ026, the efficacy of erlotinib plus bevacizumab against CNS metastasis and PE tended to be better than that of erlotinib alone (HR 0.78, 95% CI: 0.42–1.43 and HR 0.58, 95% CI: 0.34–1.02, respectively). Osimertinib has better efficacy against CNS metastases in patients with untreated EGFR-mutated NSCLC than gefitinib or erlotinib (21). Osimertinib plus bevacizumab is expected to have greater efficacy against CNS metastases.

Recently, immune checkpoint inhibitors (ICIs) have emerged as promising alternative treatments for NSCLC (22). However, a recent retrospective study found that patients with oncogenic driver mutations, such as EGFR and anaplastic lymphoma kinase (ALK), tend to display reduced responses to ICIs regarding objective response rates and PFS compared with the effects in patients with wild-type EGFR and ALK-negative cancer (23). The reason for this finding is unclear, and the therapeutic strategy of EGFR-TKI with ICIs has not been reported. Conversely, in the IMpower150 study, ICIs in combination with bevacizumab were effective against NSCLC, including lesions with EGFR or ALK genetic alterations (24). Regarding the use of ICIs for treating NSCLC featuring oncogenic driver mutations such as EGFR and ALK, further research is needed to validate the clinical biomarkers involved in the response to ICI therapy.

At present, several treatment strategies are available for

EGFR-mutant NSCLC, such as osimertinib alone, first- or second-generation EGFR-TKIs alone, EGFR-TKIs combined with bevacizumab, and EGFR-TKIs combined with platinum doublets. We must optimize these treatment strategies for patients with EGFR-mutant NSCLC. In the future, we hope to develop more efficient new-generation EGFR-TKIs or treatment strategies for patients with EGFR-mutant NSCLC.

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Footnote

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