NSCLC, locally advanced

ANTITUMOR ACTIVITY OF BEVACIZUMAB COMBINED WITH ERLOTINIB IN T790M RESISTANCE MUTATION POSITIVE NON-SMALL CELL LUNG CANCER XENOGRAFT MODELS

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Aim: Erlotinib (ERL), a specific inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase, benefits patients with non-small cell lung cancer (NSCLC), especially those with EGFR active mutations. However, progressive disease occurs when resistance is acquired by T790M mutation or MET amplification. Bevacizumab (BEV), a humanized anti-vascular endothelial cell growth factor monoclonal antibody, has been demonstrated to be effective in combination with standard chemotherapies for advanced NSCLC patients. We previously reported the promising efficacy of combining ERL and BEV in mouse models of NSCLC harboring EGFR exon 19 deletion. In the present study, we examined the antitumor activity of BEV combined with ERL in NSCLC models harboring T790M resistance mutation.

Methods: BALB-nu/nu mice were subcutaneously inoculated with NSCLC cell lines, NCI-H1975 (L858R + T790M mutation) or HCC827-EPR (exon19 deletion + T790M mutation). After randomization on Day 1, BEV (5 mg/kg) was intraperitoneally administered once a week, and ERL (75 mg/kg) was orally given daily. Antitumor activity was evaluated by tumor growth inhibition (TGI) with measuring tumor volume. In tumor tissues, phosphorylations of EGFR signaling molecules were evaluated by western blot analysis, and microvessel density was evaluated by CD31 immunohistochemistry.

Results: In the NCI-H1975 model, the TGI on Day 11 of ERL, BEV and combination was 8%, 45% and 35%, respectively. NCI-H1975 tumors were resistant to ERL, and the combination of ERL and BEV did not enhance the antitumor activity of BEV monotherapy. In the HCC827-EPR model, the TGI on Day 50 of ERL, BEV and combination was 96%, 63% and 111%, respectively. HCC827-EPR tumors exhibited significant sensitivity to ERL (p ≤0.05) in vivo, and combining the two agents showed significantly higher antitumor activity than each monotherapy (p ≤0.05). The phosphorylation levels of EGFR, AKT or ERK in HCC827-EPR tumors were suppressed by ERL. The microvessel density was significantly decreased by BEV in both models.

Conclusions: The combination treatment of ERL and BEV has the potential to be effective for ERL-responding NSCLC models with T790M resistance mutation.

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