

Abstract

Human epidermal growth factor receptor 2 (HER2) is a member of the ErbB family of receptor tyrosine kinases. Numerous studies have reported amplification and overexpression of HER2 in several types of cancer, including non-small cell lung cancer (NSCLC). On the other hand, the benefit of HER2-targeted therapy is much less well defined. In this study, we investigated the antitumor effect of neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI), against NSCLC cells harboring HER2 alterations. We examined the sensitivity of normal bronchial epithelial cells (BEAS-2B), ectopically overexpressing wild-type or mutant HER2, to neratinib. Furthermore, we examined the antitumor activity of neratinib in several NSCLC cell lines harboring HER2 alterations in vitro and in vivo experiments, and investigated the association between their genetic alterations and sensitivity to neratinib treatment. BEAS-2B cells ectopically overexpressing wild-type HER2 or mutants (A775insYVMA, G776VC, G776LC, P780insGSP, V659E, G660D, and S310F) showed constitutive autophosphorylation of HER2 by Western blotting. While these BEAS-2B cells were sensitive to neratinib, they were insensitive to erlotinib, a first-generation EGFR-TKI. Neratinib also exerted antiproliferative effects on HER2-altered (H2170, Calu-3, and H1781) NSCLC cell lines. Neratinib was also found to exert strong tumor growth inhibitory activity in mouse xenograft models of HER2-altered lung cancer cells. Our study strongly suggests the potential of neratinib as a promising therapeutic option for the treatment of HER2-altered NSCLC.