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Antitumor activity of ZD6474, a small molecule VEGF receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to EGF receptor-targeted drugs

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Tyrosine Kinase Inhibitors

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Developmental Therapeutics - Experimental Therapeutics

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Author(s):
F. Ciardiello, R. Bianco, R. Caputo, R. Caputo, V. Damiano, B. M. Veneziani, F. De Vita, S. De Placido, A. R. Bianco, G. Tortora; Seconda Universita degli Studi di Napoli, Naples, Italy; Universita degli Studi di Napoli Federico II, Naples, Italy

Abstract:

The epidermal growth factor receptor (EGFR) autocrine pathway plays a key role in cancer progression. Inhibition of EGFR signaling with gefitinib (an orally available EGFR-selective tyrosine kinase (TK) inhibitor) and C225 (an anti-EGFR MAb) causes dose-dependent tumor growth inhibition in mice with human GEO colon cancer xenografts. Clinical activity has also been shown in patients with advanced solid tumors. Vascular endothelial growth factor (VEGF) plays a pivotal role in the regulation of tumor angiogenesis and vascular permeability. ZD6474 is an orally available VEGF receptor TK inhibitor that also has activity against EGFR TK. ZD6474 treatment results in significant growth inhibition in a range of human xenograft models. In this study, chronic administration of gefitinib (150 mg/Kg/dose, days 1-5 weekly) or C225 (1 mg/dose twice weekly) in mice with established GEO xenografts effectively inhibited tumor growth, but re-growth was seen after 90 days' treatment. Continuous ZD6474 therapy (75 mg/Kg/dose, days 1-5 weekly), however, resulted in effective tumor growth inhibition until the end of the study period (140 days). ZD6474 activity in EGFR-inhibitor-resistant tumors was determined in mice pre-treated with gefitinib or C225 for 4 weeks. Once re-growth was apparent (approx. 4 weeks after therapy) animals were treated with either EGFR inhibitor again or ZD6474. Tumor growth inhibition was seen only in ZD6474-treated mice. The apparent resistance to EGFR inhibition was investigated by establishing cell lines from the re-growing GEO tumors. Western blotting revealed a 30-50% reduction in EGFR protein expression in both cell lines. No major change was observed for the EGFR ligand TGFα, or in expression of p53, p27, MDM2 and MAPK. Both cell lines exhibited increased COX-2, phosphorylated activated MAPK and VEGF protein expression. These data demonstrate that growth of EGFR-inhibitor-resistant tumor xenografts can be effectively inhibited with ZD6474. This agent may therefore inhibit tumor growth by blocking VEGF-induced vascularization and EGF-mediated cancer cell growth.

Associated Presentation(s):

1. Antitumor activity of ZD6474, a small molecule VEGF receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to EGF receptor-targeted drugs

Meeting: 2003 ASCO Annual Meeting
Presenter: Fortunato Ciardiello
Session: Developmental Therapeutics - Molecular (General Poster Session)

Other Abstracts in this Sub-Category:

1. Molecular mechanisms of resistance to the HER1/EGFR tyrosine kinase inhibitor erlotinib HCl in human cell lines.

Meeting: 2003 ASCO Annual Meeting Abstract No: 762 First Author: R. Perez-Soler
Category: Developmental Therapeutics - Experimental Therapeutics - Tyrosine Kinase Inhibitors

2. Quantitative gene expression in non-small cell lung cancer from paraffin-embedded tissue specimens: Predicting response to gefitinib, an EGFR kinase inhibitor

Meeting: 2003 ASCO Annual Meeting Abstract No: 763 First Author: R. B. Natale