Abstract

Abnormalities in gene expression and signaling pathways downstream of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) contribute to the progression, invasion, and maintenance of malignant phenotype in human cancers, including breast. Conventional chemo- and radio-therapy is widely used for treating early stage breast cancer and metastasis, which is frequently associated with overexpression of EGFR and resistance to apoptosis, leading to treatment failures and recurrence of the disease. To improve therapeutic response in patients with metastatic breast cancer, novel and combinatorial approaches are mandatory. Accordingly, one interesting and promising research direction for improving the treatment of breast cancer could be a molecular-targeted therapy against EGFR and VEGFR in association with standard therapeutic regimens. ZD6474, a dual tyrosine kinase inhibitor of EGFR and VEGFR shows antitumor activity by inhibiting ERK/MAPK and Akt/PI-3K pathways in breast cancer. It inhibits anchorage-independent colony formation as well as invasion and metastasis. In combination therapy, ZD6474 enhances the efficacy of chemotherapy (paclitaxel) and radiotherapy (UV-B) by inhibiting cell proliferation, migration and metastasis. The combination of ZD6474 with paclitaxel or UV-B versus either agent alone also more potently downregulated the anti-apoptotic bcl-2 protein, upregulated pro-apoptotic signaling events involving the expression of bax, activation of caspase-3 and caspase-7 proteins, and induced poly (ADP-ribose) polymerase cleavage resulting in apoptosis. These observations have considerable potential clinical relevance for patients with locally advanced metastatic breast cancer, where clinical studies of dose-intensive paclitaxel therapy and radiotherapy are currently in progress. Moreover, the local administration of chemotherapeutic drugs often leads to nonspecific distribution in the body via circulatory system. This resulted in cytotoxicities to normal cells other than tumor nest. Nanoparticle (AuNp) assisted drug (ZD6474) delivery system will play a crucial role in tissue and site specific drug delivery with lesser cytotoxicity and greater efficiency. The recurring problem of cancer therapies is the development of chemo-resistance. Thus, the development of chemo (paclitaxel)-resistant breast cancer cell line will help in elucidation of molecules that may be targeted to sensitize and overcome chemoresistance to conventional therapies.