PHARMACOGENOMICS OF MOLECULAR TARGETED TRAGS IN CANCER TREATMENTS

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Improved understanding of tumor biology has led to the identification of numerous growth factors that are involved in malignant transformation and tumor progression. Many of these factors induce cellular responses through receptors with intrinsic tyrosine kinase (TK) activity. Therefore, inhibiting TK receptor’s activity is one of the ways to effectively block the disordered proliferations of cancer that arise from these pathways. The human epidermal growth factor receptor (HER) family is over-expressed or dysfunctional in many human malignancies. Therefore, these receptors were identified as targets for cancer therapy. There are two mechanism of action to inhibit HER receptors. One is anti-HER-antibody, and another is HER-TK inhibitor. Several agents have been developed that reversibly, or irreversibly, inhibit one, two or all of the HER receptors. Gefitinib and erlotinib are HER1 specific TK inhibitor and lapatinib is dual HER1/HER2 TK inhibitor. Cetuximab is anti-HER1-chimeric antibody and trastuzumab is anti-HER2-human monoclonal antibody. Appropriate patient selection to identify good responders is likely crucial for revealing the clinical benefits of the HER targeted drugs. Prospective and retrospective clinical trials with non-small cell lung cancer (NSCLC) clearly show the existence of populations that are more likely to respond to gefitinib and erlotinib, including women, patients with adenocarcinoma, non-smokers and Asian patients (compared to Caucasians). Moreover, Somatic mutations in specific regions of the ATP-binding domain of HER1 have been shown to have strong associations with sensitivity to gefitinib or erlotinib. Patient selection according to the HER1 mutation status has yielded a superior response rate and survival rate by excluding patients who are unlikely to respond to gefitinib treatment. Hamilton et. al. has compared the pharmacokinetic variables of erlotinib in current smokers with nonsmokers after receiving a single dose of erlotinib. In a result, the pharmacokinetics of erlotinib is different in current smokers and nonsmokers. The observation that \( AUC_{\infty} \) and \( C_{24h} \) were significantly decreased in smokers compared with nonsmokers, and a smaller decrease in \( C_{\text{max}} \) was observed, is consistent with increased metabolic clearance of erlotinib in current smokers. Recent results of randomized phase III showed that addition of cetuximab to standard chemotherapy regimen has revealed statistically prolonged survival in advanced colorectal cancer or NSCLC. Existence of K-ras oncogene mutation is a potent negative predictive factor of response of cetuximab. Efficacy of trastuzumab has been affected by the antibody-dependent cell-mediated cytotoxicity (ADCC) activity, which correlates Fc gamma R polymorphisms. Our data in prospective study suggested that specific Fc gamma R single nucleotide polymorphisms (SNPs) have correlated response rate and survival rate of trastuzumab, suggesting Fc gamma R -mediated ADCC plays an important role in the clinical effect of trastuzumab.