Relevant Biomarkers alongside Optimal Therapy of Lung Cancer

Lung cancer is the leading cause of death in the developed countries and the second most cause of mortality in Korea. Non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases. The majority of NSCLC are diagnosed as advanced stage, with only 25-30% of the cases resectable. Platinum-based combination chemotherapy is the therapeutic cornerstone of treatment both in the metastatic and adjuvant setting, although molecularly targeted drugs are entering standard treatment in advanced stages. The response rate of standard chemotherapy is only about 30-40%, and the median overall survival is about 11-14 months in metastatic NSCLC. No specific combination has proved superior and therapeutic plateau has been reached although the overall outcomes are being improved very slowly by introduction of newly developed drugs. Because many patients do not respond to treatment for NSCLC, individualizing therapy to provide the most effective treatments is pivotal in improving survival outcome. Identification of predictive biological markers for response to specific cytotoxic agents is of considerable value to achieve the best outcomes and limited toxicities.

Of these biomarkers, excision repair cross-complementation group 1 (ERCC1) appears to be the most clinically investigated. It is the rate-limiting protein in the nucleotide excision repair (NER) and interstrand cross-link repair pathways. Impaired NER could lead to increased genomic instability and malignant phenotypic behavior. High expression of ERCC1 confers resistance to the platinum agents although its low expression is a poor prognostic factor of NSCLC without chemotherapy. Ribonucleotide reductase M1 (RRM1) is a regulatory component of ribonuclotide reductase aiding with DNA synthesis and repair, and it also mediates suppression of cell migration and metastasis. Ribonucleotide reductase is the major target of the nucleoside analogue gemcitabine, therefore its high expression is related with the gemcitabine resistance. Microtubules are very dynamic structures which are required to lengthen and shorten during cellular activities. Micotubule polymers are composed of tubulin heterodimers consisting of α- and β- protein subunits. Taxane and vinorelbine bind to β-tubulin and inhibit microtubule dynamics. Overexpression of beta-tubulin class III (βIII tubulin) is associated with resistance to paclitaxel and a poor prognosis. The best described mechanism of resistance to tubulin binding agents is multi-drug resistant phenotype (mdr-1 gene), however reduced drug binding to the αβIII tubulin dimer is also proposed as a mechanism of resistance. EGFR mutation has been spotlighted with the advent of effective EGFR tyrosine kinase inhibitors (EGFR-TKIs). Sensitizing mutations of EGFR are the most important biomarker for the response of EGFR-TKIs. Several studies have reported that patients with NSCLC harboring EGFR mutations have a more favorable prognosis than patients with wild type EGFR both in the untreated and treated cases with cytotoxic agents.

The question of which molecular markers will be the most useful for selecting drugs for individual patients remains unanswered. However, small series of studies are showing the promise about tailored therapy, which warrant prospective validation in carefully designed randomized clinical trials, using standard protocols.