

Molecular Markers to Help Individualize Therapy

Heinz-Josef Lenz, MD

USC/Norris Comprehensive Cancer Center

Los Angeles, California

Pharmacogenomic studies have been demonstrated to provide a sufficient tool in developing such strategies. Genetically determined variability of function of certain key enzymes has been shown to influence toxicity, response and survival to chemotherapy. These enzymes may be involved in metabolism, influx and efflux of anticancer-drugs and procedures influencing cell viability such as DNA-repair mechanisms. We are only at the beginning of using the knowledge of the genome and newest high-throughput technology to acquire more information to develop individualized therapies. We have evidence of germline polymorphisms as well as gene expression levels of enzymes involved in DNA repair, oxidative stress and metabolic pathway of 5-FU with clinical significance; however, these data are from small retrospective studies. It will be critical to include these functional analyses into clinical studies. To include gene expression analysis into the routine of clinical trials might be more difficult, since technologies for extraction (eg, RNA extraction from paraffin) are more complex and the technology is not broadly accessible. Meanwhile, data from cDNA micro-array analyses will supply information on other potential pathways that might have to be considered if patients are treated with fluoropyrimidines, irinotecan and oxaliplatin. In addition, genes involved in metabolism, accumulation and action of newly developed drugs like antibodies against epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) have to be screened for polymorphisms that impact the function of the gene products. One example of a possible candidate in this new field is a CA repeat polymorphism in intron 1 of the EGFR gene that affects EGFR transcription. The consequent analysis of pharmacogenetic markers in clinical settings is critical to guarantee the application and incorporation of these promising data into the clinic and to stratify patients according to their genetic make-up.