Results: This module has some major advantages: it has an intuitive work-flow based Graphical User Interface compliant with GCP requirements; provide some alerts for relevant prescribing problems as the excess/suboptimal dose or the renal impairment; has some basic statistical functions; it could be accessed on the Internet and Intranet (using a virtual server or FileMaker Pro Server™); protected and secure connection with dedicated login and password. A capture is presented in Figure 1. The most powerful quality is the capacity to provide direct, on-site and instant information about the dose-intensity for each product (function of the administered dose and the delay between two consecutive cycles). A demonstration is planned to be performed at the congress.
Conclusions: RDBMS are helpful tools in our efforts to ameliorate the efficiency of prescribing modern treatments in oncology. They are a "must" for those interested to provide a highly qualified exercise, especially in clinical research.

195 POSTER

Pharmacogenomic analysis of the peripheral blood cell transcriptome in patients with advanced solid tumors treated with the mTOR inhibitor deforolimus (AP23573; MK 8669) in phase Ib studies

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Background: Inhibitors of the mammalian target of rapamycin (mTOR), a serine/threonine kinase that integrates multiple signaling pathways and cellular processes, are undergoing extensive clinical investigation as anticancer drugs. Deforolimus (DEF) is a potent, specific, non prodrug mTOR inhibitor that is currently being investigated in a phase 3 trial in patients with metastatic sarcomas. The immediate targets of mTOR (e.g., phospho-4E-BP1) are used as biomarkers to monitor drug effects and select the optimal biologically effective doses in phase I studies. This assay, however, does not provide information on downstream cellular pathways that might be relevant to antitumor activity. Furthermore other targets, not interrogated by the assay, might contribute to the clinical activity of mTOR inhibitors. Here, we investigated in the context of two phase Ib studies with DEF (SENDO-S045AP2301−02) whether its administration was associated with specific changes in the peripheral blood transcriptome (PBT). We hypothesized that this genomic analysis could better capture the complexity of the downstream effects of mTOR inhibitors and identify more robust biomarkers for this class of drugs.
Methods: Blood samples for PBT analysis were taken from patients receiving 12.5, 37.5, 50, or 75 mg of DEF IV on day 0 and 1 of cycle 1 prior to any other therapy. Affymetrix U133 2.0 GeneChip arrays were done in a total of 16 patients (3 to 5 per dose level). Real time RT-PCR was performed to validate selected genes.
Results: We found a set of genes that were consistently modulated 24 h after administration of DEF at doses $\geqslant$37.5 mg in $\geqslant$70% of patients and up to 100% of cases. The number of commonly affected genes increased with the dose, peaking at 50 mg. At this dose, 83 and 10 transcripts were, respectively, down- and up-regulated in $\geqslant$75% of patients, with 33 transcripts down-regulated in 100% of cases. The degree of down- and up-regulation of most genes increased with the dose, showing evidence of a dose-related response at $\geqslant$37.5 mg. This was in contrast with the phospho-4E-BP1 assay in PBMCs that showed complete inhibition already at the lowest dose. Among down-regulated genes at doses $\geqslant$50 mg there was a prevalence of genes in pathways that might be functionally connected to mTOR activity (e.g., apoptosis, NK cell-mediated cytotoxicity, MAPK, insulin and Toll-like receptor signaling).
Conclusion: The PBCT can be a powerful source of information to monitor drug effects and identify robust and stringent biomarkers in phase I trials. Here, we identified genes that were consistently modulated after DEF, showed evidence of dose-dependence, and may represent clinically useful biomarkers of mTOR inhibition. These findings need to be validated in larger clinical trials. In addition, further analysis of the biological functions associated with the genes identified in PBT may reveal important aspects of the mTOR inhibitor activity.

196 POSTER

Intron 1 CA repeat polymorphism is associated with the sensitivity to EGFR TKIs in NSCLC patients with wild type EGFR

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Background: The epidermal growth factor receptor (EGFR) plays a key role in carcinogenesis and progression in various solid tumors by its activation by over-expression, mutation, and autocrine ligand production etc. Clinical outcome of EGFR TKIs is mainly affected by the mutation status of EGFR TK domain, histology, gender, smoking status and ethnicity. Recently, it has been reported that some genetic variants of EGFR gene including CA repeat polymorphism in intron 1 modulate its transcriptional activity.
We investigated the allelic frequency of three genetic variants on EGFR gene in Korean population and analyzed the genetic variants, EGFR mutations, and the sensitivity to EGFR TK inhibitors in vitro and NSCLC patients.
Methods: Genomic DNA was extracted from peripheral blood in 221 healthy volunteers and 20 NSCLC patients receiving EGFR TK inhibitors. PCR products that were amplified for promoter region, intron 1, and exon 18 21 were sequenced in a 3730XL DNA analyzer and GeneScan. For in vitro experiment, thirteen NSCLC cells and A431 epidermoid carcinoma cells (as control) were used to measure the drug sensitivity to gefitinib using the SRB assay.
Results: In healthy Koreans, the most frequent EGFR CA repeat genotype was 20/20 (32.6%) repeats followed by 16/20 (22.1%), 15/20 (8.6%) and the allelic frequencies of −216G>T and −191C>A were 95% and 99%, respectively. Among thirteen NSCLC cell lines, the most sensitive cells to gefitinib were PC9 and HCC-827 (IC50: <5 months), the sum of CA repeats was 39 40 with no mutations in EGFR.
Conclusion: Not only the distribution of CA repeat genotype but also the allelic frequency of −216G>T and −191C>A in Korean population were quite different from those of Caucasian. It is obvious that the mutations in tyrosine kinase domain of EGFR gene are the major determinant to anti-tumor efficacy of EGFR TKIs. Our results suggest that CA repeat polymorphism in intron 1 be another predictive biomarker of EGFR TKIs in NSCLC patients with wild type EGFR. Further study using sufficient human tumor samples is underway to support this preliminary results.

197 POSTER

Pathway determinants of 5-fluorouracil activity

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Background: Response to 5-fluorouracil (5-FU) varies considerably among individuals, making it desirable to identify determinants of its activity. However, findings thus far have been inconclusive. This is possibly because most studies have focused on only a few components of entire pathways of 5-FU pharmacology or studied in vitro or in vivo models in isolation. In this study, we took a pathway based approach to identify candidate determinants of 5-FU activity in cell lines and xenografts.
Materials and Methods: Total RNA was extracted from 18 colorectal cancer cell lines and 14 human colorectal cancer xenografts before 5-FU treatment. RNA levels of 91 genes involved in folate metabolism, 5-FU transport, metabolism, activity and downstream mechanisms were quantified in these samples using real-time PCR low density array analysis. Sensitivity to 5-FU was defined by IC50 values for cell lines and extent of tumor shrinkage for xenografts. Chi-square, information gain ratio, OneR and Cfs subset were used to rank genes which were differentially expressed between the sensitive and resistant cases.
Results: Five cell lines and 8 xenografts were classified as resistant to 5-FU and 16 cell lines and 6 xenografts as sensitive. In cell lines, beta-ureidopropionase (UPB1) was the most differentially expressed by all 4 statistical tests. In xenograft samples, cytidine triphosphate synthetase II (CTPS2) was ranked the most differentially expressed in 3/4 tests. In combined analysis of cell lines and xenografts CTPS2 was the top ranked