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PLENARY SESSION 5

Pharmacogenetics

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General overview of pharmacogenetics

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There are in principle 3 mechanisms by which genetic polymorphisms or rare mutations of proteins involved in the metabolism, transport and action of drugs can lead to heterogeneity in efficacy and toxicity of drugs.
Drug metabolizing enzymes, in particular cytochrome P450 enzymes play a pivotal role in the elimination process of most drugs. Variability of drug metabolism is responsible for the prononounced interindividual differences in plasma concentrations when patientd receive the same dose of a drug. As a consequence variability in drug action and side effects / toxicity ensues. During the last 30 years for many phase 1 and phase 2 enzymes catalysing the biotransformation of drugs mutations have been identified. These mutations affect either the expression or catalytic properties of these enzymes. In the case of mutations leading to a loss of function administration of a standard dose of a drug will lead to very high plasma concentrations resulting in exaggerated response, side effects or toxicity. On the other hand gene amplification of enzymes resulting in ultrarapid metabolism of drugs has been identified as a mechanism of poor response. Moreover, in the case of prodrugs which require bioactivation for therapeutic efficacy loss of enzyme function due to polymorphism of the enzyme is associated with a loss in efficacy.
But even if drug dose is individualized guided by therapeutic drug monitoring in order to achieve the same plasma concentrations substantially variability in therapeutic response and side effects will still be observed because concentrations at the site of action vary substantially. It is increasingly recognized that transfer of drugs in and out of the cells is not a passive process depending on physicochemical properties, lipophilicity and protein binding but also involves active transfer by transport proteins. These transport proteins are expressed in many tissues and affect the absorption, biliary and renal excretion of drugs. They constitute the blood brain barrier (BBB) for many drugs since they are expressed at the luminal site of the endothelial cells of the brain capillaries limiting the transfer of drugs from the blood into the CNS. For a number of these transporters genetic polymorphisms have been discovered which affect their expression. Finally, same concentration of a drug at the site of action does not necessarily mean identical response because mutations at drug targets (receptors, neurotransmitter transporters, signaling pathways) can profoundly alter response.

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Pharmacogenetic variation of UDP-glucuronosyltransferases in drug resistance and cancer

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Extensive inter-individual and inter-ethnic differences in drug glucuronidation have been reported. These variations in drug glucuronidation are caused by genetic polymorphisms and differential expression of UDP-glucuronosyltransferases (UGTs) induced by environmental chemicals.
Sixteen functional human UDP-glucuronosyltransferases (UGTs) have been identified and classified into two subfamilies based on sequence similarity. All of the UGTs are able to catalyse drug glucuronidation in vitro.
Genetic defects have been observed in the UGT-1A1 gene associated with hyperbilirubinaemia. In familial Gilbert's disease, mild hyperbilirubinaemia is caused by reduction in promoter function and expression of UGT1A1. Hyperbilirubinaemia caused by various drugs has been shown to be associated with this frequent polymorphism in the UGT1A1 gene.
Mutations and polymorphisms have also been examined in several other UGTs and linked to variation in xenobiotic glucuronidation and cancer.
Resistance mechanisms of human colon cancer to cytotoxic drug chemotherapy are poorly characterised. Two human colon cancer cell lines and two different cytotoxic agents (SN-38 the active metabolite of clinically used CPT-11 and NU/ICRF 505 an anthraquinone-tyrosine conjugate) have been used to identify a novel drug resistance mechanism caused by drug glucuronidation. The presence of UGT1A9 enzyme and activity was detected in drug resistant HT29 cells, but not in sensitive HCT116 cells. Propofol, a probe substrate for UGT1A9, competitively inhibited glucuronidation of SN-38 and NU/ICRF 505 by over 80% resulting in up to a 32 fold elevation in intracellular drug concentration. Co-treatment of cells with propofol and NU/ICRF 505 or SN-38 increased cytotoxicity by 5 and 2 fold respectively in HT29 cells. A range of UGT aglycones including food additives (methyl 4-hydroxybenzoate) and proprietary medicines (ibuprofen) were capable of inhibiting SN-38 and NU/ICRF 505 metabolism. Glucuronidation may represent a major mechanism of intrinsic drug resistance in colon cancer amenable to reversal with relatively non-toxic agents.
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Pharmacogenetic determinants of clinical outcome and toxicity in colon cancer

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We have identified predictive markers (gene expression and genomic polymorphisms) of response and survival to both fluoropyrimidines and platinum based chemotherapeutics in colon cancer. These markers include TS, DPD and TP as predictive markers for fluoropyrimidines chemotherapy and ERCC1, XPD, and GSTP1 for platinum based therapy.TS expression has been correlated with disease free survival, overall survival and is predictive of recurrence (independent of patients who receive 5-FU).The predictive value of TS has also been demonstrated to identify those patients whose tumors may respond to fluoropyrimidines, as those with low levels of TS are more likely to respond. Other markers contributing to determining the response to fluoropyrimidines based therapy include thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD). Using these markers in combination increases the likelihood in predicting whether a patient will responds to therapy. Interesting a genomic polymorphism in the 5' UTR region of TS also predicted response to 5-FU based chemotherapy as well as toxicity to protracted infusion of 5-FU and Xeloda.Recently, newer platinum drugs specifically oxaliplatin have shown significant activity in colorectal cancer. The expression levels of genes found to be vital in platinum metabolism have revealed potential markers to predict responses. With the use of intratumoral gene expression of ERCC1 and genomic polymorphisms of ERCC-1, XPD and GSTP-1, we were able to predict response and survival in patients with colon cancer treated 5-FU/oxaliplatin. The capability of an almost absolute prediction of non-response as well as identification of a set of patients with very high but not absolute probability of response has a significant impact on the design of new treatment regimens with fluoropyrimidines and platinum. Tumors with high TS, TP and DPD expression levels should be treated with non-TS directed anticancer drugs such as CPT-11 or oxaliplatin, or in combination with 5-FU. Patients with high expression of ERCC1 should be treated with non-platinum based regimens whereas patients with low levels would be good candidates for cisplatin or oxaliplatin. With the development of new effective anticancer drugs such as CPT-11 and oxaliplatin, it is of clinical significance to better understand the metabolism and the mechanism of resistance of these new active agents. It is essential to understand why some patients develop life-threatening toxicity and why some tumors are resistant to CPT-11 or oxaliplatin.

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Pharmacogenetic determinants of toxicity and response in acute lymphoblastic leukemia

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Childhood acute lymphoblastic leukemia (ALL) has long served as a model for a drug-responsive cancer. Using chemotherapy alone, event-free survival rates of 80% have been achieved. However, there remain subtypes of ALL with more refractory disease, and these high cure rates are not without serious long-term risks. Our work has focussed on trying to improve cure rates for ALL while minimizing serious adverse effects of therapy, which include second cancers, avascular necrosis of the hip, neurotoxicity, cardiotoxicity, sterility, severe obesity, and hepatotoxicity. Interindividual differences in susceptibility to these adverse effects are due to an interplay between the manner in which treatment is delivered and the underlying susceptibility of the host. Germline polymorphisms in genes responsible for the disposition, metabolism, and responsiveness of the host and of the leukemic blasts are likely to account for some of host variabil-