Young Oncologists session
Genetics for treatment tailoring

101 INVITED

Genetic polymorphisms and cancer treatment: general concepts

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The Human Genome Project has led to the discovery of a surprisingly high number of DNA sequence variants, the majority of them being single-nucleotide polymorphisms (SNPs). SNPs have attracted the attention of scientists because of the potential influence of DNA sequence variation on the susceptibility of patients to the activity and/or adverse reaction of cancer chemotherapy. For these reasons, new disciplines, pharmacogenetics and pharmacogenomics, are gaining momentum and their application to current cancer treatment and drug discovery is a high priority.
The number of studies reporting a relationship between DNA sequence variants and treatment outcome, disease recurrence and survival are continuously increasing in number. In particular, the following associations were found: DPD gene mutations and severe 5-FU toxicity [1], activating mutations of EGFR and responsiveness of NSCLC to gefitinib [2], NER polymorphisms and recurrence after treatment for superficial bladder cancer [3], ERCC1 polymorphisms and severe drug toxicity in NSCLC patients [4], genetic variants in the UGT1A1 gene and severe neutropenia by irinotecan [5], MTHFR genotype and treatment response in pediatric ALL [6], TS and MTHFR gene polymorphisms in normal tissue and 5-FU sensitivity [7], and TPMT genotype and early treatment response to 6-MP in childhood ALL [8]. The next step in pharmacogenetic research should be the validation of these findings in randomized prospective trials, specifically designed to compare the outcome of treatment selected on the basis of patient's genotype (normal tissue vs. tumor) with standard approach. In conclusion, the improvement in genotyping technologies and the availability of a high-density SNP maps, combined with efficient and cost-effective analytical methods, open the possibility of fulfilling the promise of reducing the toxicity burden and personalize the treatment for cancer patients.

References

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102 Abstract not received

103 INVITED

Phenotype as a surrogate for genotype

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The availability of multiple systemic therapies highlights the importance of identifying the characteristics of patients and tumors that are associated with resistance or susceptibility to toxicity to specific agents. Such profiling represents an opportunity to optimize rational treatment selection. Pharmacogenetic polymorphisms represent an important field to explore to account for interpatient variability in efficacy and toxicity. A realistic hope is to explain the unexpected link between cutaneous rash and tumor sensitivity to EGF receptor antagonists by a pharmacogenetic polymorphism of the receptor. However, polymorphisms in genes remain constant throughout a person's lifetime while several critical factors influencing the cellular response to cytotoxic-induced DNA damages have considerable variations with time. Therefore, obvious limitations to pharmacogenetics are the role of epigenetic alterations in cancer cells, and the role of aging and cachexia in normal cells. To illustrate to assess the phenotype, we will show the role of Cytochrome P450 activity on the docetaxel clearance using a midazolam test as a probe, and the role of cachexia on the occurrence of febrile neutropenia.

104 Abstract not received

Scientific Symposium
New molecular targets

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107 INVITED

Hypoxia inducible factor-1 as a novel target for cancer drug development

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Hypoxic cancer cells are found in all solid tumors in regions where tumor growth outstrips new blood vessel formation. Hypoxic cancer cells are resistant to chemotherapy and radiation and are a major reason for the failure of current cancer therapy. The hypoxia inducible factor-1 (HIF-1) is a transcription factor that is an important regulator of the growing tumor's response to hypoxia. HIF-1 activity in tumors depends on the availability of the HIF-1α subunit whose levels increase under hypoxic conditions or through constitutive mechanisms. HIF-1 activates genes that allow the cancer cell to survive and grow in the hostile hypoxic tumor environment. Increased tumor HIF-1α has been correlated with increased angiogenesis, aggressive tumor growth and poor patient prognosis, leading to the current interest in HIF-1α as a cancer drug target. A number of anticancer agents have been reported to decrease HIF-1α or HIF-1 transactivating activity in cells in culture and a variety of mechanisms are proposed. Some of the agents are moving towards clinical trial. It will be important to demonstrate that the agents inhibit HIF-1α in patient tumors or, failing this, the downstream consequences of HIF-1 inhibition such as decreased vascular endothelial growth factor formation, and relate this inhibition to antitumor activity. Only in this way will it be possible to determine if HIF-1α is a valid cancer drug target in humans.

108 INVITED

TGF-beta inhibitors

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Advances in the study of the molecular mechanisms that govern tumour progression are providing hopeful and, in some cases, dramatic therapeutic benefits in cancer and have pushed rational molecular targeting to the cutting-edge of cancer therapy. Among several other signal transduction pathways, the TGFbeta pathway is nowadays been evaluated as a potential therapeutic target. TGFbeta is a multifunctional cytokine that regulates tissue homeostasis and development. In normal epithelial cells, TGFbeta is a very potent anti-proliferative factor that, strikingly, becomes an oncogenic factor in some malignant tumours by inducing proliferation, angiogenesis, invasion, metastasis and suppressing the immune response. The role of TGFbeta in oncogenesis has prompted the development of therapeutic strategies based on the inhibition of the TGFbeta pathway. Several studies have highlighted the therapeutic potential of antagonizing the TGFbeta pathway, mainly in metastatic breast cancer and glioma. Large molecule TGFbeta signalling inhibitors based on antisense oligonucleotides or neutralizing antibodies are being used in clinical trials and small molecule TGFbeta-receptor-kinase inhibitors have proved successful in pre-clinical studies. Work using murine models of cancer has shown lack of toxicity associated with anti-TGFbeta drugs. However, the TGFbeta response can be an anti- or pro-tumorigenic response depending on the tumour stage and type. This dual role of TGFbeta in oncogenesis presents a unique challenge that has to be addressed to be able to select the patient population that may benefit from an anti-TGFbeta therapy. The understanding of the malignant transformation of TGFbeta will improve patient stratification and the development of successful therapeutic strategies. In order to unveil the molecular mechanisms involved in the switch of the TGFbeta response towards malignancy, we focused our studies on glial tumours. The screening of patient derived tumour biopsies and glioma cell lines for TGFbeta activity showed that in some gliomas, TGFbeta promotes proliferation whereas in others, it inhibits proliferation. Using microarray analysis to dissect this differential response, we obtained a list of candidate factors that could be involved in the induction of proliferation by TGFbeta. We found a tight correlation between some of those candidate factors and the induction of proliferation by TGFbeta in glioma tumours and proved that they are mediators of the TGFbeta oncogenic response.