role of pharmacogenetics in metabolizing enzymes (UGT1A1 and CYP2D6 respectively) seems important. However, if dosing based on these specific pharmacogenetic differences between patients will be truly successful remains controversial, as many non-inherited factors and other single-nucleotide polymorphisms may also influence the metabolism of these anti-cancer drugs. For instance, co-medication is capable to induce or to inhibit the activity of CYP3A4, a crucial enzyme involved in the metabolism of many drugs. Therefore, a 'phenotyping' dosing strategy might potentially be more promising than a 'genotyping' dosing strategy that is focussed on pharmacogenetic variability only. But also this phenotyping strategy has serious limitations. In this presentation differences between both dosing strategies will be discussed based on recent literature.

12 INVITED

Pharmacogenetics of drug transporters

R. Danesi[1]. [1]*University of Pisa, Department of Internal Medicine, Pisa, Italy*

Membrane transporters are major determinants of the absorption, distribution and elimination of many drugs. Functional genomic and clinical studies have provided new information regarding the contribution of coding variants in transporters to drug disposition and response. ATP-binding cassette (ABC) genes play a role in the resistance of malignant cells to anticancer agents. The ABC gene products, including ABCB1 (P-glycoprotein), ABCC1 (MRP1), ABCC2 (MRP2, cMOAT), and ABCG2 (BCRP, MXR, ABCP) are also known to influence oral absorption and disposition of a wide variety of drugs. As a result, the expression levels of these proteins in humans have important consequences for an individual's susceptibility to certain drug-induced side effects, interactions, and treatment efficacy.
The influence of polymorphisms in ABCB1 2677G>T/A, 3435C>T, and 1236C>T and progression-free and overall survival in patients treated with paclitaxel/carboplatin demonstrated that, compared to homozygote GG carriers at 2677, women with the minor T/A alleles were significantly less likely to relapse following treatment (Hamidovic et al., 2010). In a study on patients with androgen-independent prostate cancer given docetaxel and thalidomide, subjects receiving docetaxel alone and carrying the 1236C-2677G-3435C linked alleles had improved overall survival after treatment. Additionally, patients treated with docetaxel and thalidomide carrying the 2677T-3435T haplotype had a shorter median survival. Among both treatment arms together, individuals carrying the 2677GG genotype also had a significantly longer time to neuropathy. Finally, there was a strong trend toward patients carrying the 2677TT-3435TT diplotype having higher grades of neutropenia. Therefore, this study demonstrated that docetaxel-induced neuropathy, neutropenia grade, and overall survival could be linked to ABCB1 allelic variants with ensuing negative implications for docetaxel treatment in patients carrying ABCB1 variant genotypes (Sissung et al., 2008). A study investigated the relationships of polymorphisms in transporter genes ABCB1, ABCC2, and ABCG2 and CYP2D6 to clinical outcome of patients with hormone receptor-positive breast cancer receiving tamoxifen. CYP2D6 variants were significantly associated with shorter recurrence-free survival in patients with two variant alleles compared to subjects without variant alleles. Among 51 tag-SNPs in transporter genes, a significant association was found at rs3740065 in ABCC2 (in patients with AA vs. GG genotypes). The number of risk alleles of CYP2D6 and ABCC2 showed cumulative effects on recurrence-free survival. Thus, polymorphisms in CYP2D6 and ABCC2 are important predictors for the prognosis of patients with breast cancer treated with tamoxifen (Kiyotani et al., 2010). In conclusion, drug transporters play an important role in cancer chemotherapy and the full evaluation of their implication in stratified medicine should be assessed in prospective trials.

References

Hamidovic A, et al. Clinical significance of ABCB1 genotyping in oncology. J Oncol Pharm Pract 2010; 16: 39.

Sissung TM, et al. ABCB1 genetic variation influences the toxicity and clinical outcome of patients with androgen-independent prostate cancer treated with docetaxel. Clin Cancer Res 2008; 14: 4543.

Kiyotani K, et al. Significant effect of polymorphisms in CYP2D6 and ABCC2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. J Clin Oncol 2010; 28: 1287.

13 INVITED

The role of gene expression profiling in early drug development

S. Loi[1], C. Sotiriou[1]. [1]*Jules Bordet Institute, Breast Cancer Translational Research Laboratory, Brussels, Belgium*

The advent of high through-put, whole genome gene expression profiling has increased our understanding of the molecular heterogeneity of many cancers. From a breast cancer viewpoint, the identification of distinct molecular subtypes has resulted in the majority of clinical trials no longer being conducted in the global population, but in subgroups such as ER+, HER2+ or triple negative disease (ER−/HER2−). Similarly, gene expression signatures have emerged as potential new prognostic tools and chemotherapy response predictors.
The potential role of gene expression profiling in early drug development is immense. Discovery of previously unidentified molecular subtypes can also provide information on the biology such as potential drug targets and biological pathway enrichment. Gene expression profiles induced by drugs may also provide an indication of the transcriptional phenotype most likely to respond. The importance of serial biopsies in early drug development has also begun to emerge as baseline biopsies may not provide the full picture with regards to prediction of response. Serial biopsies can also provide demonstration or confirmation of the molecular mechanisms of action of the new agent and highlight mechanisms of potential resistance. In breast cancer, several neoadjuvant clinical programs are running around the world to take advantage of the accessibility of serial biopsies in the early stage setting. Finally, gene expression profiles may be helpful as predictive biomarkers of response to drug therapies. These 'functional read-outs' may be more sensitive, objective and quantitative than a single marker by immuno-histochemistry, for example p-AKT or p-S6 but as yet, there has been no clinical validation of this concept.

14 INVITED

Genomic versus histological grading in soft tissue sarcomas

J. Coindre[1], F. Chibon[2]. [1]*Institut Bergonié, Anatomo-cyto-pathologie, Bordeaux, France;* [2]*Institut Bergonié, Pathology, Bordeaux, France*

For more than 20 years, histological grading has been the most important factor for predicting metastasis-free and overall survival in adult soft tissue sarcomas. The most common grading systems used are the National Cancer Institute grading and the French grading. The last system is based on a score obtained by evaluation of 3 parameters: tumor differentiation, mitotic rate and amount of tumor necrosis. The main value of grading has been for the most efficient use of chemotherapy. However, histological grading has several limitations: its reproducibility is questionable, it is not applicable to all types of sarcomas and it is not informative for grade 2 tumors which represent about 40% of sarcomas. Moreover, the value of grading is also limited by the universal use of core needle biopsies. Histological grading can be considered as a morphological translation of molecular events that determine tumor aggressiveness and we postulated that molecular parameters will be important for prognostication of sarcomas. In order to set up a molecular grading, we performed a genomic and expression profiling (array-CGH and Affymetrix) of 183 sarcomas with complex genetic profile and established an expression signature which is highly predictive of metastasis outcome in the whole group and the different subgroups such as limb sarcomas and leiomyosarcomas. This signature has been established by a bottom-up supervised strategy using genomic profile (array-CGH), histologic grade and a previously published chromosomal instability signature. The resulting signature is composed of 67 genes related to mitosis and chromosome management (CINSARC for Complexity Index in SARComas). This signature has been validated on an independent group of 127 sarcomas with complex genetic profile. It appears to be superior to the French grading system with no intermediate group. It has been tested in silico in GIST, breast carcinomas and lymphomas and it could be an important tool in GIST for selecting patients for adjuvant target therapy. Moreover, metastatic potential seems to be related to tumor complexity level and driver genes related to genome complexity could become therapeutic targets. In conclusion, the concept of grading should be maintained, histological grading is still useful in complement to tumor histotype/genotype but molecular grading should be developed and tested in sarcomas and GIST.

15 INVITED

Microarray and validation analyses performed on melanoma metastases identify TYRP1 as a prognostic marker for both DMFS and OS

G. Ghanem[1], L. van Kempen[2], H. Id Booufker[3], M.D. Galibert[4], M. Wiedig[1], A. Theunis[5], F. Salès[6], G. Laurent[7], A. Awada[8], F. Journé[1]. [1]*Institut J. Bordet, Lab of Oncology and Experimental Surgery, Brussels, Belgium;* [2]*Radbout university Nijmegen Medical Center, Pathology, Nijmegen, The Netherlands;* [3]*Institut J. Bordet, Lab of Oncology and Experimental Surgery, Brussels, Belgium;* [4]*University of Rennes 1, CNRS UMR 6061, Rennes, France;* [5]*Institut J. Bordet, Pathology, Brussels, Belgium;* [6]*Institut J. Bordet, Surgery, Brussels, Belgium;* [7]*University of Mons, Histology, Mons, Belgium;* [8]*Institut J. Bordet, Medical Oncology, Brussels, Belgium*

Using microarrays in 32 skin and lymph node metastases, we generated a 278 gene probe signature based on a survival cut-off of 30 months.