

Wednesday, 17 November 2010 08:00–09:45

WORKSHOP 1

Characterising the target for improved drug tailoring

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INVITED

Assessing target functionality for drug and patient tailoring: a clinical perspective

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The ultimate aim of the treatment of cancer is to find the best possible drug or treatment, in the most optimal condition, for the individual cancer patient. This does not mean that treatment can only be based on an individual basis, but that we should try to identify the characteristics of patient (sub-) populations that fit best to the characteristics of the drug or treatment. Molecular biology achievements have enabled us over the last decade to more precisely identify these characteristics and develop better tailored drugs. On the other hand we should also acknowledge that the success rate of biomarker driven development is relatively limited. In that sense it is fascinating to see the number of definitions one can find in the literature on "biomarker". Evidently, we need to better define the topic of our discussion on biomarkers.

From the perspective of drug development, assuming that a molecular change leads to the occurrence of cancer, there may be 3 milestones with key questions: (1) does the drug affect the target (molecular change), which identifies proof of mechanism, (2) does the effect on the target lead to a change in tumor biology, which identifies proof of principle, and (3) does the signal of change in tumor biology lead to a clinical evidence of absence of tumor growth, or even of tumor size regression and ultimately improve (progression free- or overall-) survival, which would be the proof of concept. To each of these one could link a biomarker that signals the effect.

Since either form of survival is a long term endpoint, and therewith unattractive for drug development evaluation, a lot of resources have been spent in finding so called surrogate markers for ultimate clinical outcome. Particularly in this scenario we have not been very successful. The examples of successful use of biomarkers are in the selection of patient populations based on proof of mechanism and proof of principle. If these can be ensured, apparently there is a high likelihood that proof of concept will follow. This is exemplified in the development of agents such as imatinib, herceptin, and more recently GDC-0449, PF-02341066 (Crizotinib) and some others.

A case will be made that drug development should be focussing on these selection-biomarkers, predictive for effect, rather than the late prognostic ones that have been used for a while now.

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INVITED

Pharmacodynamic markers of targeted agents

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Abstract not received

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INVITED

Pharmacoeigenetics and epigenetic drugs

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Recent years have seen the mapping of increasing numbers of genes in which promoter CpG islands are hypermethylated in cancer. Such DNA-methylation mapping has revealed unique profiles of hypermethylated CpG islands that define each neoplasia. For the various cancers for which DNA-methylation profiles are available, CpG-island hypermethylation has been used as a tool to detect cancer cells in all types of biological fluid and biopsy. Another interesting aspect correspond to pharmacoeigenetics: DNA methylation as a predictor of response to chemotherapy. The most compelling evidence that epigenomic profiles can predict responses of cancer to therapy is provided by the methylation-associated silencing of the DNA-repair protein MGMT in human brain tumours. MGMT is directly responsible for reversing the addition of alkyl groups to the guanine base of DNA and this base is the preferred point of attack in the DNA of several alkylating chemotherapeutic drugs, including BCNU (carmustine), ACNU (nimustine), procarbazine, streptozotocin and temozolamide. MGMT hypermethylation is the best independent predictor of response to BCNU and temozolamide in gliomas. The potential of

MGMT to predict the chemoresponse of human tumours to alkylating agents can also be extended to other drugs with similar modes of action, such as cyclophosphamide. Most importantly, one of the essential differences between human cancer genetics and epigenetics is that DNA methylation and histone modification changes are reversible under the right circumstances. Thus, epigenetic alterations are one of the weakest points in the defences of the cancer cell, because those hypermethylated tumour-suppressor genes in their long "sleep" can be awoken and reactivated with the right drug regimens and exert their normal growth-inhibitory functions. Two families of epigenetic drugs, DNA-demethylating agents and inhibitors of histone deacetylase, have emerged as the most promising compounds in this area, and several pharmaceutical compounds have received approval for the treatment of hematological malignancies.

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INVITED

Biosample collection in clinical trials

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Access to biological materials (BM) in both sufficient quantity and quality is considered one of the key bottlenecks hindering successful bench to bedside translation. However, this does not need to be the case. Clinical trials offer a unique opportunity in which to collect biological materials; large, multi-centred studies often containing randomized treatment and control arms, administration of novel drugs and drug combinations, combined with high quality clinical data and patient follow up. Biological materials collected in this context provide a valuable opportunity to address study designs for biomarker discovery and validation that would be difficult to fulfill from community or population based BM collections alone.

Due to the multidisciplinary nature, integration of biological materials collection into clinical trials warrants careful upfront planning and input from a range of expertises. Currently, the EORTC is building on its existing experiences and expertise gained from specific initiatives, the EORTC Virtual Tumour Bank and also EORTC Group activities and is further developing new mechanisms to support investigators with the practical aspects of collection, storage and access to biological materials.

As much as possible the BM collection should be integrated into standard clinical practices and must be made as simple as possible to facilitate the collection. To aid this integration of BM collection in EORTC clinical trials, a checklist has been developed involving the key areas of up front statistical planning and clear biomarker research objectives, biosample quality requirements and ethical and practical restrictions, which are increasingly important to successful translational research, and combines these into a simple tool for practical use. Identifying and managing key risk areas early in clinical study set up can lead to maximizing the BM collection success and efficient trial set up.

Wednesday, 17 November 2010

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WORKSHOP 2

Pharmacogenetics and pharmacogenomics in cancer

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INVITED

To genotype or to phenotype: that's the question

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In our goal to personalize anti-cancer treatment, many different dosing strategies have been suggested over the years. Earlier, for most anti-cancer drugs, dosing based on body-surface area solely has been proven ineffective to lower the inter-individual pharmacokinetic variability (IIV). A more tailored therapy should lead to a clinically relevant decrease in IIV and should ultimately create a minimum amount of serious side effects and a maximal therapeutic effect in individual patients.

Extremes in patients' capacity to metabolise the drug of interest may be the result of pharmacogenetic variability, as undeniably shown for the enzyme thiopurine S-methyltransferase (TPMT) in the metabolism of azathioprine. But also in the metabolism of irinotecan and tamoxifen, the

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 anticancer 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.

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INVITED

Pharmacogenetics of drug transporters

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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

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INVITED

The role of gene expression profiling in early drug development

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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.

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INVITED

Genomic versus histological grading in soft tissue sarcomas

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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.

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INVITED

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

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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.