Monday, 24 September 2007

Opening session (Mon, 24 Sep, 09:00−10:30)

1 INVITED

Translating basic research into patient benefit: The druggable cancer genome

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The progressive unravelling of the mysteries of the cancer genome, and in particular the identification of the mutations and epigenetic abnormalities that drive the malignant phenotype, provides previously unprecedented opportunities for basic and translational research. One of the key areas in which our knowledge of the cancer genome and resultant hijacked signal transduction pathways is being best exploited is targeted drug development. Although drug discovery remains technically challenging, it is increasingly possible to develop molecular therapeutics that act on deregulated cancer gene products. Progress has been particularly impressive in the development of drugs, both antibodies and small molecules, acting on kinases. Many kinase inhibitors are highly selective whereas others showed a broader pattern of activity. Given that most cancers are likely to be driven by several molecular abnormalities, and also recognising that the development of drug resistance clearly remains a major problem even with the new molecular therapeutics, it can be argued that optimal therapy will require combinatorial therapeutic approaches. These can be designed rationally to attack multiple points of intervention, either on the same target, at different points on the same oncogenic pathway, or on distinct pathways. They can also be selected to attack different biological effects or hallmark traits of cancer. In addition to carefully constructed cocktails of highly selective molecular therapeutics, drugs that act on multiple molecular targets, or on multiple therapeutic targets downstream of a single but broadly influential target, offer alternative therapeutic options. Examples of the latter include the molecular chaperone HSP90, the proteasome or chromatin modifying enzymes such as histone deacetylases. In addition, combinations of molecular therapeutics with cytotoxic agents will also find utility. Strategic and technical approaches to drugging the cancer genome will be illustrated by our work the discovery of inhibitors against targets such as HSP90, PI3 kinase, AKT/PKB, CDKs, B-RAF and chromatin modifying enzymes. The focus of the talk will be on the overcoming the current challenges by integrating new approaches to targets, technologies and treatments. Particular emphasis will be placed on molecular biomarkers as we move towards the vision of personalized molecular cancer medicine.

Supported by Cancer Research UK

2 INVITED

Moving cancer treatment into the 21st century

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Introduction: Exploiting the great knowledge acquired in the 20th century about cancer genes to develop both molecular biomarkers and molecular therapeutics forms the basis for the development of personalized cancer medicine in the 21st century.

In simple words, finding the right treatment for the right patient at the right time is the greatest challenge oncologists are facing nowadays.

We will take the example of early breast cancer (BC) therapy to illustrate the most striking clinical advances already accomplished as well as future directions for clinical and translational research.

Selection of adjuvant systemic therapies: historical perspective: Our oldest adjuvant treatment modalities – chemotherapy and tamoxifen – have first been evaluated in "high risk" patients, namely those harbouring large tumors with nodal involvement, without too much attention paid to the biological features of the primary tumor.

The definitive proof of their benefit to women with early breast cancer was brought by the Overview in the 1980's. An important progress was accomplished when the tamoxifen Overview data were dissected according to estrogen receptor (ER) status: while ER "rich" tumors derived an important benefit from tamoxifen, this benefit was virtually inexistent in ER "poor" tumors. A first window into the world of "targeted" therapies had been opened . . .

The IBCSG investigators were the first to attempt a "dissection" of the chemotherapy effects and to show marked heterogeneity in the magnitude of chemotherapy benefit between ER "absent" tumors and ER "rich" tumors, with the former showing much enhanced benefit. These observations were based on retrospective, exploratory analyses, done first in the context of IBCSG clinical trials and later in the context of the Overview. The latter, however, failed to isolate a subset with "no benefit" and suffers, in addition, from the pooling of a large variety of chemotherapy regimens, some of which are no longer in use today. As a result, the majority of oncologists continue to prescribe chemotherapy with "risk" as the target!

Trastuzumab had a much easier "route" to the field of tailored adjuvant therapies: from the start, its testing was restricted to the right population, namely women with HER2 overexpressed / amplified tumors, a factor that has undoubtedly contributed to its success.

The St-Gallen 2005 meeting introduced a fundamental change in the treatment allocation paradigm: "first select the target in the tumor . . . then think about risk, using the latter to assess trade-off between anticipated efficacy and toxicity". We will propose that this paradigm is the corner-stone of modern "tailored" adjuvant therapy. While recent progress has been done in evaluating "risk", much work still needs to be done in identifying the Achilles' heel of each tumor for therapy selection.

Multi-gene prognostic signatures on their way to the clinic: Fairly reliable gene-expression signatures predicting BC outcome have been developed in the last few years. A recent meta-analysis of publicly available gene-expression and clinical data totaling 2833 breast tumors provides 3 strong messages:

1. The published multigene signatures, despite the disparity in their gene lists, show similar prognostic information.
2. Proliferation is the biological process that has the strongest impact on clinical outcome, at least for the first few years following loco-regional therapy.
3. Tumor size and nodal status retain their prognostic information in a multivariate model.

However, strong claims about the clinical value of these signatures cannot be made without prospective clinical trials that validate their benefit above and beyond the use of standard clinico-pathological prognosis variables.

Two gene expression predictors, namely the 21-gene recurrence score (ONCOTYPE DX) and the 70-gene Amsterdam signature (MAMMAPRINT®) have reached the final step of prospective clinical trial testing.

In the MINDACT trial, 6,000 node-negative early breast cancer patients will have their risk assessed through standard clinical-pathological factors and through the new prognostic tool Mammaprint. To bring homogeneity and standardization to the risk assessment done in the control arm, this will be done through a modified version of the Adjuvant Online! program. Three scenarios are possible: (a) both methods classify the patient as high risk and, in this case, chemotherapy will be proposed; (b) both methods classify the patient as low risk and, in this case, chemotherapy will not be proposed; (c) the methods are discordant in their results and the patient will be randomized between "follow the genomic risk results" or the standard method. With this design it is estimated that 10 to 20% less patients will be spared adjuvant chemotherapy without any negative impact on their outcome, with obvious advantages for the patients and for health care systems.

In the TAILORx trial, 10,500 node-negative ER+ early breast cancer patients will be screened and have their risk assessed by the Oncotype Dx score. Patients with a score bellow 11, an estimated 29% of the population, will be proposed endocrine therapy only. Patients with a recurrence score higher than 25, an estimated 27% of the population, will be proposed chemotherapy in addition to endocrine therapy. The remaining 44% of the patient population (about 4,500), with a recurrence score between 11 and 25 will be randomized between endocrine therapy alone and chemo plus endocrine therapy. This is a non-inferiority design trial, where a decrease in 5-year DFS rate from 90% (with chemo) to 87% (without chemo) is defined as unacceptable.

The prediction is that these trials, TAILORx and MINDACT, will demonstrate a real improvement in the clinician's ability to evaluate prognosis, with a subsequent reduction in over- and under-treatment of women with adjuvant chemotherapy.

Aiming at the target: The development of adjuvant endocrine therapy has taught us 4 lessons: 1) the target plays a critical role; 2) it is important to measure the target accurately; 3) the duration of therapy matters; 4) progress depends on understanding modulators of the target.

Oncogenic redundancy, indeed, is recognized today as a significant obstacle to the success of targeted treatment and calls for "combinatorial and sequential therapies".

The development of high throughput platforms, which can provide parallel information on thousands of tumor genes and their correspondent proteins and the use of "synthetic lethality screens" in preclinical experiments should help with the identification of critical pathways and lead to smart combinations and/or sequences of targeted therapies.

A new dimension in the search for the right target: the stem cell: Gene-expression profiling studies have brought new information in the areas of breast cancer classification, prognosis and prediction of response to therapy.

Multigene prognostic "signatures", in particular, have taught us a critical lesson: not all the relevant information related to outcome is contained in the primary tumor gene expression profile. The Amsterdam and the Rotterdam prognostic signatures do carry strong prognostic information

for the first 5 years following surgery ... but lose their prognostic power beyond year 5.
This observation calls for the need to reinforce the study of circulating tumor cells and disseminated tumors cells, which constitute a window into the metastatic process ... and a potential way of grasping the biology of putative breast cancer stem cells.
If the cancer stem-cell theory is confirmed, it will be important to identify, among CTC and DTC, which cells are capable of generating metastases. Genotyping and phenotyping of these cells should provide insight into the metastatic process and should lead to the discovery of new therapeutic targets.
The need for a revolution in the design and conduct of cancer clinical trials: As science is now catching up with clinical needs, a profound revolution needs to take place in the way clinical trials are being designed, conducted and financially supported. The trials should no longer be designed for the whole BC population, but indeed, should be tailored at relevant molecular subtypes. A much more intense cross-talk with basic scientists needs to occur – early on – with molecular hypothesis (for example of reduced or enhanced treatment benefit) being incorporated upfront and served by adequate statistical power.
Every possible effort at gathering patient and tumor material has to be implemented, given the parallel development of a variety of high-throughput genomic and proteomic platforms that should allow for a much more comprehensive picture of the biology of the tumor as well as the particularities of the host.
The ensuing costs of these "clinical-omic" trials will be substantial but this is the price today for moving from increasingly expensive empirical oncology treatments to tailored therapies that might be cost-saving in many instances.
The financial burden of these clinical-omic trials of the 21st century should be shared by governments, health insurance companies and pharmaceutical industry.

Monday, 24 September 2007

Symposium (Mon, 24 Sep, 10:45−12:45)
Angiogenesis and vascular targeting

3 INVITED

Signalling pathways as targets for therapy in angiogenesis and metastasis

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Cell motility, proteolysis and interactions with extracellular matrix (ECM) underpin angiogenesis and invasion, key determinants of tumour progression. These processes provide a rich source of molecular targets for cancer therapy as inhibitors may restrain both angiogenesis and metastasis with activities complementary to cytotoxic therapies. Oncogenic receptor tyrosine kinases (RTK) and angiogenic RTK such as VEGFR-2 on endothelial cells (EC) and VEGFR-3 on lymphatic endothelial cells (LEC) activate signaling cascades including phosphatidylinositide 3-kinase (PI3K), phospholipase C (PLC)g and mitogen activated protein kinases (MAPK). We are exploring the therapeutic potential of inhibitors of these pathways in in vitro functional assays and human tumour xenograft models. PI3K antagonists inhibited chemomigration and haptotaxis of a wide variety of tumour cells in vitro and downregulated specific matrix metalloproteinases and angiogenic cytokines. Novel inhibitors also showed activity in human tumour xenografts (including orthotopic, metastatic models) with clear downregulation of biomarkers of response. Tumours with activated PI3K pathways due to PTEN loss, upregulated RTK or P110a mutations were equally sensitive. The compounds also inhibited EC proliferation, migration, tubular differentiation in vitro and tumour angiogenesis in vivo indicating, as predicted, additional indirect therapeutic effects. Secondly, we showed that PLCg1 plays a major role in tumour cell and EC motogenic responses to both activated RTK and ß1 integrins. Validation of PLCg1 as a therapeutic target was obtained using stable and inducible RNAi vectors in vitro and in vivo in an orthotopic, metastatic prostate carcinoma xenograft model. We are now developing inhibitors of this potential new therapeutic target, and will aim to disable both PLCg and PI3k pathways since there is evidence of compensatory activation. Heat shock protein 90 (HSP90) chaperones key oncogenic proteins, and inhibitors can thus effectively and simultaneously disrupt several parallel signalling pathways. 17AAG downregulated client proteins in human tumour cells and EC and inhibited haptotaxis, chemomigration, invasion and uPA production. In vivo, EC client proteins (including all three VEGF receptors) were downregulated by 17AAG and inhibition of growth and metastasis of human tumour xenografts was associated with reduced microvessel density. Future work will identify optimal combinations of novel inhibitors for the prevention and treatment of disseminated disease.

4 INVITED

Clinical anti-angiogenesis

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Angiogenesis, the formation of new blood vessels, has been validated as a target in several phase III clinical trials in which conventional chemotherapy with or without inhibitors of VEGF has been compared. Studies in colorectal cancer, renal, breast and non-small cell lung cancer have demonstrated a survival advantage in favour of combination therapy. While, most of these results have been associated with the anti-VEGF antibody, bevacizumab, recent data in hepatocellular and renal carcinoma have demonstrated a survival advantage with oral VEGF receptor tyrosine kinase inhibitors, highlighting the potential of this class of molecule.
It is clear that VEGF is a valid target in oncology and that VEGF inhibitors have a vascular mode of action. However, this is a complex issue as it appears that anti-angiogenic drugs might have a direct effect on blood vessels as well as on circulating endothelial cells and their precursors. There is an additional confound in that VEGF inhibitors might also have an anti-tumour effect.
There remain significant questions about the optimum use of VEGF inhibitors. For instance: VEGF inhibitors are postulated to cause reductions in vascular permeability, normalization of the vasculature and reductions in interstitial pressure. These parameters are potentially important in terms of scheduling of combination therapy. On the other hand in the single agent, maintenance therapy of cancer it is not clear how long to continue therapy and in particular whether we should continue treatment beyond progressive disease. Indeed the mechanisms of escape from VEGF inhibitors are being defined now and this will be an important area for future research.
Emerging data have shown that combinations of VEGF and EGF inhibitors can induce significant anti-tumour response rates in heavily pre-treated patients, prompting the question of how active these non-cytoxic regimens will be in the first line setting. One problem with this approach is the cost of combination therapy and it will be critical to establish biomarkers that predict benefit or progression so that these drugs can be used optimally. Finally, as new classes of anti-angiogenic agents emerge we will need to focus on their mechanisms of action of the compounds to ensure that particular pathways are optimally inhibited.

5 INVITED

Role of haematopoietic cells in tumour angiogenesis: from discovery to targeted cancer gene therapy

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We recently described a population of monocytic cells characterized by the expression of the Tie2 receptor (Tie2-Expressing Monocytes, TEMs). These TEMs specifically home to tumours and promote tumour angiogenesis and growth. Remarkably, the selective elimination of TEMs by a Tie2-driven suicide gene completely prevented human glioma neovascularization in the mouse brain and induced substantial tumour regression (De Palma et al., Cancer Cell 2005). In this model, TEM elimination did not affect myelopoiesis, nor it prevented recruitment of other haematopoietic populations to the tumours, suggesting that TEMs represent a distinct lineage of proangiogenic monocytes. To substantiate this concept, we used cell sorting and real time PCR-based low-density arrays to compare the gene expression profile of TEMs with that of other tumour-infiltrating and tissue-derived myeloid cells. We found that although TEMs have typical features of tumour monocytes/macrophages, a significant fraction of the interrogated genes were differentially expressed in TEMs vs. tumour macrophages. Some of these genes have critical roles in angiogenesis, tissue remodelling and immunity, which suggests that TEMs may also create an immune-privileged environment that promotes tumour growth. Remarkably, we identified Tie2-expressing monocytes also in human peripheral blood and cancer, suggesting that these cells may have a role in human pathology, possibly representing a novel pharmacodynamic marker to monitor angiogenesis or new targets of anti-cancer therapies.
Given their marked tumour-specificity, TEMs might be used as selective gene delivery vehicles for the transport of gene therapy to tumours.