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.