of topo IIA, we are still far from the use of this marker in current practice because we need proof of principle trials. To this end, two large studies are ongoing. The first of these two studies aims to perform a meta-analysis of four clinical trials which have compared an A-based regimen to CMF in the adjuvant setting. Tumor samples from patients entered in these four trials will be centralised and HER-2 and topo IIA gene status will be evaluated.The second study aims to test prospectively the predictive value of topo IIA in a group of approximately 400 patients with large operable endocrine-resistant BC treated with pre-operative single-agent epirubicin. These two ongoing studies might have an impact on future standard practice.

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New endocrine agents

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Oestrogens are the dominant hormonal stimulant for breast cancer growth. For many years the antioestrogen tamoxifen has been the first line endocrine therapy for patients with early or late stage steroid receptor positive breast cancer, and as such it has resulted in a reduced mortality from the disease. Laboratory data suggest that the partial agonist activity of tamoxifen creates a limit on its efficacy and a possible mechanism for acquired resistance. These concepts supported the development of aromatase inhibitors which block the synthesis of oestrogens in post menopausal women. These agents do not bind to the oestrogen receptor (ER) and therefore possess no oestrogenic activity. Additionally a new type of steroidal antioestrogen (fulvestrant) has been developed that down regulates ER levels and also lacks any agonist activity. Recent clinical data have revealed that 3rd generation aromatase inhibitors are more effective in advanced disease than tamoxifen. Also the aromatase inhibitor, anastrozole has shown greater efficacy than tamoxifen or a combination of the 2 in the adjuvant setting. Ongoing adjuvant trials of aromatase inhibitors involve more than 40,000 patients. Fulvestrant has been found to be similar in efficacy to anatrozole in advanced disease. The immediate challenges are to maximize the benefit from these new agents and to investigate their optimal use in combination with agents that target growth factor pathways that may mediate resistance.

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Lymphangiogenic growth factors and tumor metastasis

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Angiogenesis and permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two receptors VEGFR-1 and VEGFR-2. The VEGFR-3 receptor does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have found that homozygous VEGFR-3 targeted mice die around midgestation due to failure of cardiovascular development. We have also purified and cloned the VEGFR-3 ligand, VEGF-C. Transgenic mice expressing VEGF-C show evidence of lymphangiogenesis and VEGF-C knockout mice have a lymphatic vascular phenotype. The proteolytically processed form of VEGF-C binds also to VEGFR-2 and is angiogenic. VEGF-D is closely related to VEGF-C, similarly processed and binds to the same receptors. Thus VEGF-C and VEGF-D appear to be both angiogenic and lymphangiogenic growth factors. VEGF-C overexpression led to lymphangiogenesis, intralymphatic tumor growth and lymph node metastasis in several tumor models. Furthermore, soluble VEGFR-3, which blocked embryonic lymphangiogenesis, also blocked lymphatic metastasis in breast and lung cancer models.

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Angiogenesis and tumour pathophysiology

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A solid tumor is an organ comprised of neoplastic cells and host stromal cells nourished by the vasculature made of endothelial cells - all embedded in an extracellular matrix. The interactions among these cells, and between these cells, their surrounding matrix, and their local microenvironment, control the expression of various genes. The products encoded by these genes, in turn, control the pathophysiologic characteristics of the tumor. The tumor pathophysiology governs not only the tumor growth, invasion and metastasis, but also the response to various therapies. In my presentation today I will discuss insights revealed by intravital microscopy (IVM) into the molecular, cellular, anatomical and physiological workings of tumors and how these insights have facilitated the development of improved strategies for cancer detection and treatment. I will focus largely on the work done in my laboratory on the role of host-tumor interactions in the integrative pathophysiology of tumors,and convey the following points: Tumor vessels are abnormal in their organization, structure and function. These abnormalities contribute to heterogeneous vascular permeability, blood flow, and microenvironment. Tumor interstitial matrix is formed by proteins secreted by host and tumor cells as well as those leaked from the nascent blood vessels. Tumor interstitium is heterogeneous with some regions fairly permeable while other regions are difficult to penetrate. Relaxin can permeabilite the tumor matrix. Interstitial hypertension is a hallmark of solid tumors, and results from vessel leakiness, lack of functional lymphatics, and compression of vessels by proliferating cancer cells. Cancer therapy is plagued by two major problems – physiological resistance to drug delivery and oxygen, and genetic and epigenetic mechanisms driven drug resistance. Anti-angiogenic therapy has the potential to overcome these problems. Furthermore, judicious application of this therapy can normalize the tumor vessels and make them more efficient for delivery of oxygen and drugs. Combined anti-angiogenic and conventional therapies appears promising in the clinic. References: R.K. Jain,et al. Nature Review, 2002 R.K. Jain, et al, Science, 2002 R.K. Jain, et al, Nature Medicine, 2003

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Vascular targeting trials

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Tumour vascular targeting therapy exploits differences between normal and tumour blood vessels with the aim of reducing blood flow to the tumour sufficient to cause tumour cell death. Although it is considered different from anti-angiogenic therapy where the main aim is to prevent the development of new tumour vessels, it is becoming increasingly apparent that both types of therapy have overlapping activities. Differences between tumour blood vessels and normal vessels relates, partly to their immaturity which is associated with a different cytoskeleton and lack of pericytes and smooth muscle, partly to their chaotic distribution and, partly to their endothelial surface which may have a different integrins and cadherins. The distinguishing feature of vascular targeting agents in-vivo is that they induce haemorrhagic necrosis of tumours within hours of administration. Unless they have additional anti-tumour activities they are unlikely to induce major tumour responses when given alone, as the tumour cells closest to normal tissue will obtain their blood supply from that tissue. However major tumour regression is seen in vivo when combining vascular targeting agents with cytotoxic chemotherapy, radiotherapy or radiolableed antibodies.

The lack of expected responses with single agent vascular targeting agents has required the development of surrogate endpoints to determine if they are acting on their intended target. Serial dynamic MRI scans are most frequently used to obtain a pharmacodynamic endpoint, as serial PET scanning requires short half life isotopes from an adjacent cyclotron to measure blood flow.

Dynamic scans have confirmed that many of the following drugs act as vascular targeting agents in patients. 5,6-Dimethylxanthenone-4-acetic acid (DMXAA) is thought to act through local TNF induction. Four tubulin binding agents Combretastatin A4P (CA4P), AVE8062A, ZD 6126, and ABT-751 are in the clinic with CA4P having progressed to combination trials. These agents have a very different toxicity profile to cytotoxic chemotherapy. Only when the combination trials are completed will we know whether the therapeutic window is sufficient to induce major tumour regressions with acceptable toxicity.