125 INVITED

If you do not have a laboratory, then turn your clinic into one!

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In an ideal world all cancer treatment centres would be co-located with research laboratories. Clinicians and laboratory scientists would meet regularly and collaborative translational research projects would be commonplace.
In this presentation examples are provided of detailed sets of clinical observations (made in isolation from the laboratory) that have contributed to the understanding of the mechanisms of radiation injury to normal tissues and tumours.
There remains much to observe and learn in the clinic. Do not be discouraged from doing this just because there is no laboratory next door!

126 INVITED

New drug treatment for cancer in 2007 – real progress at last?

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We have become accustomed in recent years to hearing about major progress in cancer treatment as a result of rational drug development providing molecular targeted therapy linked to specific signalling pathways in certain cancers. How does this translate into the daily practice of one of Europe's largest Phase I clinical trials units?
The Drug Development Unit at the Royal Marsden Hospital sees over 500 patients per year for consideration of experimental treatment, and at least half will enter one of over 20 Phase I trials. These include both single agent and combination approaches with all forms of solid tumours treated.
Is there a changing trend in expectation of efficacy?
Over the past 2 years, our trials have indeed been marked by an increasing number of patients showing major benefit. Two key examples which are set to change clinical practice and illustrate different points are (a) AZD 2281 which is an inhibitor of Poly(ADP-Ribose) Polymerase1 (PARP1). We have recently completed the first oral continuous Phase I trial of this agent. This showed it to be well tolerated, and we demonstrated significant activity in patients with BRCA-associated (ovarian) cancer, precisely bearing out preclinical data indicating the exquisite sensitivity of these repair-deficient cancer cells. (b) Abiraterone, which is an inhibitor of the enzyme CYP 450 C17. This results in complete inhibition of androgen synthesis in prostate cancer cells and adrenal cortex while preserving other adrenal hormone biosynthesis. Our Phase I trial (continuous oral administration) showed it to be well tolerated and the drug has shown major activity in patients with so-called 'hormone-refractory' prostate cancer.
Other instructive examples where clear radiological regression has been seen include patients with refractory cancer treated with AZD 2171 (VEGFR inhibitor), BIBW 2992 (ErbB family inhibitor), PXD101 (HDAC inhibitor) and a Combrestatin A-4P/Bevacizumab combination approach to anti-angiogenesis.
The potential for significant future benefit is considerable. However, it is important to emphasize that advances in molecular diagnostics, through which the careful selection of patients most likely to benefit can be made, will be essential in order that expensive new therapies can be brought into general clinical utility.

127 INVITED

Translational reseach is key in clinical trials: MD/PhDs in the driving seat . . .

A.M.M. Eggermont. *The Netherlands*

Abstract not received.

128 INVITED

Experimental evaluation of anti-angiogenic strategies to improve outcome after fractionated radiotherapy

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Tumour development and growth depends on angiogenesis, i.e. the formation of new blood vessels. Numerous molecules have been identified to control tumour angiogenesis and therefore represent promising targets for cancer therapy. Expression levels of these molecules as well as other parameters related to tumour vasculature are important prognostic factors for radiotherapy suggesting that angiogenesis significantly contributes to radiation resistance of tumours. Molecular compounds targeting tumour angiogenesis have been demonstrated to reduce tumour growth but are not curative in themselves. Yet, radiotherapy is highly effective in sterilizing clonogenic tumour cells. Furthermore, recurrences after high radiation doses arise from a few surviving clonogenic tumour cells. Thus, even if anti-angiogenic compounds have no curative potential in themselves they may interfere with mechanisms of radiation resistance in tumours and thereby may result in important improvement of local tumour control after radiotherapy. However, impaired tumour vascularisation after anti-angiogenic intervention might be harmful because of increased hypoxia. Therefore, a thorough experimental as well as clinical validation of the combination of anti-angiogenic compounds and fractionated radiotherapy is essential.
Experimental data indicate that inhibition of angiogenesis can improve efficacy of irradiation. In the vast majority of experiments, tumour growth delay was used as endpoint and simultaneous combination schedules of irradiation and inhibitors of angiogenesis were tested. The increased efficacy of a simultaneous combination observed in most experiments has been attributed to a direct radiosensitizing effect of anti-angiogenic compounds on endothelial cells. A potential hazard of this combination is the possible increase in tumour hypoxia and thereby radioresistance. Experiments exploring the impact of anti-angiogenic interventions on tumour hypoxia gave controversial results. We have demonstrated that inhibition of multiple angiokinases was effective to reduce tumour angiogenesis but had no effect on the radiobiological fraction of clonogenic tumour cells.
In experimental tumours adjuvant administration of inhibitors of angiogenesis, i.e. after the end of fractionated irradiation, resulted in a prolonged tumour growth delay even in tumour models where the inhibitors alone or given simultaneously to irradiation were not effective. Enhanced sensitivity of radiation-damaged blood vessels against inhibitors of angiogenesis due to up-regulation of target receptors expressed on endothelial cells seems to be the underlying mechanism. These experiments clearly indicate that the schedule of the combination importantly determines treatment efficacy. Despite clear-cut effects on tumour growth delay observed in most experiments, data on local tumour control after fractionated irradiation are inconsistent. Thus, further investigations into the underlying mechanisms are essential to define and exploit the potential of anti-angiogenic strategies to improve outcome after radiotherapy.
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Symposium (Wed, 26 Sep, 09:00−11:00)
Congenital paediatric disorders: What do we learn from nature?

129 INVITED

Cancer-associated congenital disorders along the Ras-pathway: from genetics to novel therapeutic strategies

Abstract not received.

130 INVITED

Novel insight into the pathogenesis of dyskeratosis congenita: how defective ribosome activity can cause cancer and disease

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X-linked Dyskeratosis Congenita (X-DC) is an inherited disorder characterized by bone marrow failure, skin abnormalities, and cancer susceptibility caused by point mutations in the DKC1 gene. The DKC1 gene encodes for an enzyme that modifies ribosomal RNA (rRNA) through the site-specific conversion of uridine to pseudouridine, guided by small nucleolar RNAs. The molecular mechanisms by which impairments in rRNA modifications contribute to X-DC pathogenesis remain unknown. We utilized an unbiased proteomics strategy to identify mRNAs that were translationally impaired as a result of reductions in rRNA modifications in hypomorphic Dkc1 mutant mice, which recapitulate the clinical features of X-DC. While general protein synthesis was found to be unaffected, subsets of cellular mRNAs containing an internal ribosome entry site (IRES) element within their 5′UTRs were translationally impaired. These genes included the tumor suppressor p27 and the anti-apoptotic factors XIAP and Bcl-xL, which were specifically impaired at the level of IRES-dependent translation in Dkc1 mutant mice as well as X-DC patient cells. Moreover, we provide genetic evidence that impairments in IRES-mediated translation of p27 may contribute to the cancer susceptibility phenotype of X-DC. In order to understand the molecular mechanisms by which Dkc1m ribosomes are defective in IRES-mediated translation, we tested whether viral IRES elements that directly