and their links to cancer, together with relevant examples of regulation of their functions, will be presented.

Scientific Symposium (Tue, 22 Sep, 14:45–16:45)
Investigating novel targets and anti-angiogenic agents in brain tumours

158 INVITED

Anti-EGFR and anti-angiogenic therapy – from mice to men

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The development and clinical evaluation of therapeutic agents directed against the epidermal growth factor receptor (EGFR) or against tumor angiogenesis are two major strategies in targeting malignant gliomas. EGFR is overexpressed in approximately 60% of primary glioblastomas, frequently associated with *EGFR* gene amplification, and the constitutively active EGFRvIII variant is expressed in about half of the amplified cases. Specific EGFR targeting has been achieved using small molecule tyrosine kinase inhibitors (TKIs), such as erlotinib (Tarceva®) and gefitinib (Iressa®), as well as monoclonal antibodies (mAbs), such as cetuximab (Erbitux®). Erlotinib and gefitinib are the most well studied anti-EGFR agents. Xenograft studies in mice suggested that glioblastoma sensitivity to erlotinib is associated with the expresson of amplified and aberrant EGFR combined with wild-type PTEN. However, while two clinical studies found some evidence that a subset of patients with coexpression of EGFRvIII and wild-type PTEN or with high expression of wild-type EGFR and low levels of p-Akt respond to TKIs, a larger randomized EORTC trial detected no clinical benefit for erlotinib and no association with molecular markers. Using a highly invasive orthotopic mouse model with patient-derived xenografts, we found that response to local treatment with cetuximab depended on the presence of amplified and/or mutated EGFR, whereas the PTEN or p-Akt status was irrelevant. A recent phase II study showed that a small subgroup of patients with recurrent malignant glioma may benefit from cetuximab (administered i.v.), but response did not correlate with EGFR copy number. Promising results were recently reported for a vaccination approach, using a peptide that spans the EGFRvIII fusion junction. Phase I and II trials showed that this treatment led to T- and B-cell immunity in patients, eliminated tumor cells expressiong EGFRvIII, and caused an unexpectedly long patient survival.
Most anti-angiogenic strategies target the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) system, which is crucial to angiogenesis and edema formation in malignant gliomas. Xenograft studies showed that anti-VEGF and anti-VEGFR mAbs could strongly inhibit glioblastoma growth and prolong survival, however, treatment led to increased tumor invasion along the host vasculature. The most well studied anti-angiogenic compound is bevacizumab (Avastin®), a neutralizing mAb against VEGF. Bevacizumab has shown encouraging antitumor activity in combination with irinotecan, however this effect may be restricted to radiographic response and prolongation of progression-free survival, without prolongation of overall survival. Contrast-enhanced MRI can easily overestimate the effect of anti-angiogenic treatment, since it relies on extravasation of the contrast agent, which is impeded by the vascular permeabilty-reducing, anti-edematous effect of Bevacizumab. Nevertheless, strong subjective patient improvement and a steroid-sparing effect are clear benefits. Interestingly, tumor recurrence patterns after Bevacizumab treatment appear to confirm studies in rodents, since glioblastoma recurrences in humans are also more infiltrative. Ongoing larger randomized trials will show whether this represents a true increase in tumor cell invasiveness or a relative suppression of enhancing tumor growth, and they will further show whether Bevacizumab alone or in combination can prolong overall survival.

159 INVITED

PTEN and growth factor receptor targeting in glioblastoma

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There is compelling evidence in a variety of human cancers that activating mutations in signal transduction pathways can result in tumor cell "dependence" on the mutant pathway and predict clinical response to pathway inhibition. In some of these diseases, clinical responses have been so consistent that the main challenge is no longer to achieve an initial treatment response, but to understand, overcome, and delay the emergence of acquired resistance to these agents. Progress with targeted cancer therapeutics has been slow in glioblastoma. When used as single therapy in molecularly unselected patient populations, most signal transduction inhibitors have produced radiographic responses in only a small fraction of patients. Mechanisms of resistance to specific signal transduction inhibitors in glioblastoma are largely unknown. My presentation will discuss molecular mechanisms of resistance to signal transduction inhibitors in glioblastoma, in particular PTEN-associated resistance to EGFR kinase inhibitors.

161 INVITED

Combining the adhesion pathway inhibition with radiotherapy – from the bench to the clinic

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Background: Tumor response to radiotherapy is controlled by many intracellular tumoral factors whose deregulation leads to the modulation of the tumoral radiosensitivity, but also by micro-environmental factors such as hypoxia. These factors such as growth factors and their receptors and their downstream pathways can be intrinsically activated in some tumor cells leading to radioresistance, in particular via the inhibition of radiation-induced cellular deaths. These pathways are activated by irradiation, amplifying the phenomena of resistance by the activation of the radiation-induced DNA beaks repair, by the induction of tumoral repopulation, or stimulation of the migration pathways. Thus, irradiation activates receptors such as EGFR, FGFR, or avb3 and avb5 integrins involved in adhesion and angiogenesis, known to control tumor radioresistance via the induction of hypoxia, the control of tumor radiosensitivity via that of the endothelial cells, and its importance in the radioresistant tumor stem cells survival.
Methods and Results: We and other have shown that irradiation activates avb3/avb5 integrins, which are highly expressed in glioblastoma (GBM). Our lab has recently demonstrated that irradiation activates these integrins, which in turn control radioresistance in GBM cells via the integrin linked kinase (ILK) and RhoB under its farnesylated form, leading to the inhibition of the radiation induced mitotic death. These factors are moreover implicated in the control of the tumor micro-environment, particularly in angiogenesis and hypoxia. We have shown that the avb3/avb5 integrins, control intracellular radioresistance but also hypoxia *in vivo* and the regulation of HIF-1a via the focal adhesion kinase and RhoB, HIF-1a being a factor of radioresistance which is also activated by irradiation. Inhibition of this pathway leads to radiosensitization, normalization of hypoxia and angiogenesis. Moreover, we have shown in an other tumor that the co-expression of b3 integrin and FGF-2 was associated with a worse local control after radiochemotherapy, demonstrating the clinical relevance of this pathway in the control of the radiosensitivity.
Thus, one of the strategies to improve the radiosensitivity of radioresistant and hypoxic tumors as GBM consists in the association with the radiotherapy of inhibitors of these pathways. We and others have shown that the integrin inhibitor cilengitide induced a radiosensitization of GBM cells and xenografts. We have shown that inhibiting the farnesylation of RhoB led to radiosensitization, reoxygenation and normalization of the vasculature in GBM models. These results led us to design and conduce clinical phase I and II trials in GBM associating the farnesyltransferase inhibitor tipifarnib to radiotherapy showing good tolerance and encouraging results. An early phase trial associating cilengitide to radio-chemotherapy has shown promising results, in patients presenting the MGMT promoter methylation, probably due to a normalization of the vascularization obtained by cilengitide.
Conclusions: The optimal sequences of association between these targeted drugs and the radiotherapy remain incompletely elucidated and need to be studied. The precise study of the mechanisms of action of these therapies and of their interaction with radiotherapy, as well as the follow-up by metabolic imaging, of the patients accrued in such trials, will allow the determination of the optimal schedule of these promising combined treatments.

Scientific Symposium (Tue, 22 Sep, 14:45–16:45)
Clinical management of the elderly

162 INVITED

Geriatric assessment in oncology: a tool to provide better cancer care in the elderly

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The aging population is characterized by an extreme diversity in terms of clinical, functional and social status. As a consequence, life expectancy in

older cancer patients is influenced not only by the tumor itself but also by the various comorbidities and geriatric problems associated with old age. The health status of each older individual should be evaluated in order to optimize cancer decision making in this age group.
Oncologists are aware of a procedure for detecting older patients whose health problems may interfere with cancer treatment. Multidimensional geriatric assessment (MGA) addresses the major concerns of geriatric assessment (GA), i.e. patients' physical and mental status, their social, environmental and economic situation, their functional status, and geriatric syndromes. The MGA process involves a trained interdisciplinary team usually including a nurse and a geriatric-trained oncologist or a geriatrician, and sometimes a physical therapist, a dietician, a social worker, a pharmacist and a psychologist. Patients' health problems are detected through different validated screening tools: Katz's Activities of Daily Living and Lawton's Instrumental Activities of Daily Living scales; Cumulative Illness Rating Scale for Geriatrics; Timed Up & Go test or Performance-Oriented Assessment of Mobility instrument; Folstein's Mini Mental Status Examination; Geriatric Depression Scale; Mini Nutritional Assessment; medication review and appraisal of potential drug interactions. The findings from these tests provide a better picture of older patients' health status before cancer treatment decision making.
Nevertheless, the MGA approach requires geriatric skills that are hardly available in conventional oncology units. Thus, specific screening tools are currently being developed to help oncologists differentiate healthy senior adults from patients whose problems might interfere with cancer treatment and who require more in-depth GA. These instruments must be easy to administer and quick to complete, and not require geriatric resources.
The French National Cancer Institute has sponsored a prospective study, ONCODAGE, to validate an innovative geriatric screening tool designed to identify older cancer patients requiring GA before cancer treatment decision-making. The screening tool called G8 is composed of one question about the patient's age and 7 items from the Mini Nutritional Assessment instrument. Results of a pilot study have shown that a total score lower than 14 out of 17 indicates that the patient needs a full GA procedure. G8 will also be compared with the VES-13 instrument and a set of validated geriatric screening tools described earlier.
A total population of 1650 newly diagnosed cancer patients will be included in around 15 centres over a 1-year period. Preliminary results are expected by the beginning of 2010.
In conclusion, older cancer patients require both cancer and geriatric assessments. The more efficient model could be a two-step procedure including a preliminary screening test followed by a true GA for older patients identified as frail or vulnerable. This approach allows to characterize the patient's health status and to offer appropriate cancer treatment options. Consistent guidelines on cancer treatment in the elderly should be issued after the GA process is standardized.

163 INVITED

Radiotherapy in older patients for early breast cancer

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With the age related rise in incidence of breast cancer and the raising of the upper age limit of the UK breast screening programme to 69 years, the number of patients potentially eligible for adjuvant irradiation has risen dramatically over the last decade. However exclusion historically of patients over the age of 70 from clinical trials has led to a dearth of level 1 evidence on the role of postoperative radiotherapy (RT). The Oxford overview provides information on over 24,000 women treated with adjuvant radiotherapy (1) for operable breast cancer. However only 550 (9%) of the 6097 patients with axillary node negative breast cancer treated by breast conserving surgery were over the age of 70.
Despite the evidence that older patients can tolerate RT (2), there is evidence that the receipt of radiotherapy falls with age (3), irrespective of comorbidity status and stage of disease. The use of RT fell from 77% to 24% in women with no comorbid conditions between the ages of 65−69 and 80 years or older. A study from the SEER database of 29,760 women aged 65 or older diagnosed between 1991–2002 and treated by breast conserving surgery (BCS) showed that 22,207 (75%) received radiotherapy. Patients were more likely to receive radiotherapy if they lived in urban areas, were white, married and had fewer comorbidities.
There are few level 1 data on the impact of adjuvant RT after BCS in older patients. In women over the age of 70 the absolute risk reduction for 5 year ipsilateral breast tumour recurrence rate was smaller (11% vs 22%) compared to women under the age of 50 (1). The CALGB trial showed that in women 70 years or older with TI, NO hormone receptor positive tumours that adjuvant RT reduced the 5 year risk of IBTR from 4% to 1% (4). The difference was modest but statistically significant ($p < 0.001$). The international PRIME 2 trial (target accrual 1300 patients) is currently assessing the omission of postoperative RT in low risk (T1−2 [<3 cm], MO) hormone receptor positive breast cancer after BCS and adjuvant endocrine therapy (5). The EORTC 22881–10882 boost trial has provided level 1 evidence of the value of a boost dose after BCS and whole breast RT. The absolute of benefit of the boost in reducing the 10 year IBTR rate is smaller in women over the age of 60 (3.5%) (7.3% vs 3.8%, $p = 0.008$). A boost should offered to all fit older patients.
Shorter hypofractionated dose fractionation regimes are more convenient for older patients. Recent evidence from the START trial (6) demonstrates equivalent 5 year local control with 40 Gy in 15 daily fractions to 50 Gy in 25 fractions. A total of 11.5% of the patients in the trial were over the age of 70.
There is a paucity of data on the impact of postoperative whole breast RT on quality of life. The PRIME trial showed no overall difference in global quality of life using the EORTC QLQ C30 and QLQ B23 modules when RT was omitted in a low risk group of T1−2, NO, MO axillary node negative patients at follow up of 15 months (7).
The role of partial breast irradiation (PBI) in older patients remains investigational. Level I evidence is needed to validate this approach in this age group.
No trial of postmastectomy radiotherapy has been conducted exclusively in older patients. The survival advantage in the DBCG 82c trial in patients treated with adjuvant PMRT and tamoxifen only emerged after 5 years. Patients with 4 or more involved axillary nodes should be considered for PMRT if they have a life expectancy in excess of 5 years. The role of postmastectomy RT in women with 1−3 involved nodes or node negative with other risk factors is uncertain and under investigation in the BIG 2−04 MRC/EORTC SUPREMO trial (8).

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164 INVITED

Clinical management of the elderly: surgery

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The risk of developing cancer increases with age. The elderly population is growing world wide as a result of medical advances. Consequently, the incidence of cancer within the geriatric population is set to rise. It is predicted that cancer will soon become the leading cause of death, with over half of new solid cancer cases occurring in patients $\geqslant 70$. This epidemiological shift explains the progressive change in the clinical setting, where surgical wards are frequented by elderly patients more than previously. Surgeons are more often having to decide upon whom they should operate. Surgery, the treatment of choice for most solid tumours, carries associated risks of mortality and morbidity which increase with age due to several factors including a reduced physiological reserve and co-morbidities. However, these should not preclude surgical treatment as it has been shown that neither the number nor the gravity of associated medical conditions correlate with operative death and complications.
Life expectancy is very important in tailoring treatment plans but it is not a reliable prognosticator of the outcomes of cancer surgery. The decision whether to treat should not be based on age alone; a careful multi-dimensional pre-operative assessment is needed. Pre-operative assessment by means of Comprehensive Geriatric Assessment (CGA) defines individualised operative risk. CGA assesses a variety of areas where elderly patients often present problems (impaired functional