

is still incomplete, making it difficult to assess downstream components involved in tumor progression.

Materials and Methods: As a model system, we have used the U87MG glioblastoma cell line retrovirally transfected to express three different levels of EGFRvIII. Employing a mass spectrometric strategy previously developed in our laboratory, we have quantitatively measured global tyrosine phosphorylation events in these cell lines.

Results: This has allowed us to obtain a systems view of signaling networks initiated by the EGFRvIII receptor. We have identified many critical signaling proteins which are differentially tyrosine phosphorylated as a function of increasing EGFRvIII levels, in particular, PI-3 kinase and the cellular migration/invasion machinery. In addition, pathways normally activated by wildtype EGFR, such as the MAP kinase cascades are not responsive to EGFRvIII. K-means clustering of the phosphoproteomic data revealed a cluster of phosphorylation sites which are highly responsive to the expression levels of EGFRvIII. These include tyrosine phosphorylation sites in the activation loop of the c-Met receptor, PLC- α and pyruvate kinase 3. We chose the c-Met receptor as an example for target validation. Analysis of c-Met phosphorylation in the presence of an Anti-HGF antibody indicates that the activation of c-Met is ligand independent. Temporal treatment of EGFRvIII expressing cells with AG1478, an EGFRvIII tyrosine inhibitor, shows that c-Met activation is a result of both a direct crosstalk with the EGFRvIII receptor and the upregulation of c-Met receptor expression levels by EGFRvIII signaling. Treatment of EGFRvIII expressing cells with SU11274, a c-Met specific inhibitor, led to a dose-dependent decrease in cell growth and increase in apoptosis.

Conclusions: Our data suggests that the c-Met receptor may be an alternative target in the treatment of EGFRvIII positive tumors and establishes phosphoproteomic analysis by mass spectrometry as a means of drug target discovery.

122

INVITED

The oncogenic role of TGF-beta in glioma

J. Seoane, Hospital Universitario Vall d'Hebron, Medical Oncology Program/Institutió Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

TGF-beta acts as a tumour suppressor in normal epithelial cells and early stage tumours, and becomes an oncogenic factor in advanced tumours. The molecular mechanisms involved in the malignant function of TGF-beta are not fully elucidated. The oncogenic role of TGF-beta has prompted the design of several compounds to be used as anti-TGF-beta therapies in cancer. Importantly, the dual role of TGF-beta in oncogenesis presents a unique challenge that has to be addressed to be able to select the patient population that may benefit from an anti-TGF-beta therapy. The understanding of the molecular mechanisms of TGF-beta action and the discovery of predictors of TGF-beta response is required for patient stratification and the development of a successful therapeutic strategy. In some glioma tumours, TGF-beta acts as an oncogenic factor. We have demonstrated that high TGF-beta-Smad activity is present in aggressive, highly proliferative gliomas and confers poor prognosis in patients with glioma and we have discerned the mechanisms and molecular determinants of the TGF-beta oncogenic response using a transcriptomic approach and analyzing primary cultured patient-derived tumour cells, patient-derived glioma stem cells, and human glioma biopsies.

Special session (Wed, 26 Sep, 09:00–11:00)

The European Society for Therapeutic Radiology and Oncology (ESTRO)

123

Klaas Breur award

Hypofractionated radiotherapy in early breast cancer and implications for intensity modulated radiotherapy

J. Yarnold, The Institute of Cancer Research, Academic Unit of Radiotherapy, Sutton, United Kingdom

The rationale for 2.0 Gy fractions (F) in curative radiotherapy is based on the assumption that cancers are less sensitive to radiotherapy (RT) fraction size than late responding normal tissues. The implication is that the therapeutic ratio is highest if 2.0 Gy fractions are used. Between 1986–98, the Royal Marsden Hospital/Gloucestershire Oncology Centre Trial tested the hypothesis that fewer larger fractions may be safe and effective in breast cancer. The trial randomised 1410 patients between 50 Gy in 25 F and two 13-F regimens testing 3.0 Gy or 3.3 Gy over 5 weeks. By interpolating between 13-F schedules, the adjusted estimate of a/b for local tumour control was = 2.7 Gy (95% CI -0.2–5.7), comparable to that of late reacting

normal tissues. An independent test of breast cancer response to fraction size is expected from the UK START Trials A & B (N=4451).

If the high fractionation sensitivity of breast cancer is confirmed, the implications are that fewer, larger fractions may have significant advantages in this setting. Since it is unlikely that 13 fractions represent the limit of what might be achieved, further studies are underway, including the UK FAST Trial testing a 5-fraction regimen in which 50 Gy in 25 F is compared with two test schedules delivering 5 fractions of either 5.7 Gy or 6.0 Gy once per week. Ultimately, it is conceivable that a 5-fraction regimen delivered in 5 days will be identified that is at least as safe and effective as a standard 25-fraction regimen. If so, this provides a secure biological basis for intensity modulated radiotherapy adjusting fraction size, rather than fraction number, according to tumour relapse risk. Randomised trials are underway in the UK aiming to test this approach. These findings also stimulate research into the cell and molecular basis of fractionation sensitivity. The molecular correlates of these processes may involve DNA damage repair systems and cell cycle checkpoint controls. If the molecular mechanisms are understood, it may be possible to identify a tumour phenotype that allows modification of the dose prescription accordingly. This is an ambitious objective, but individualisation of fractionation may become possible as a result.

124

Emmanuel van der Schueren award

How progress in radiotherapy is changing oncology over time

J.W.H. Leer, Radboud University Nijmegen Medical Centre, Department of Radiation Oncology, Nijmegen, The Netherlands

Since my entering the specialty of radiotherapy in 1976 as a resident I have seen a substantial progress in the field with a great impact on oncology. For this multidisciplinary meeting I will focus on those areas my present department has contributed to.

The increased use of chemotherapy and more aggressive surgery changed the role of radiotherapy in lung cancer by reducing the number of patients presented for radiotherapy in the last 1–2 decades. However, the recently published results of the IIIA EORTC Lung Cancer Trial published by Van Meerbeeck and my late collaborator Kramer, showed that after response to induction chemotherapy radiotherapy should be considered the preferred locoregional treatment instead of surgery. So, the role of radiotherapy in these patients is re-established. In addition, a substantial number of patients still need palliative radiotherapy. In a small but randomised study we demonstrated that for patients for whom cure is no longer the aim of treatment, 10×3 Gy is better than 2×8 Gy.

There is an ongoing debate about the preferred treatment for prostate cancer. Our department demonstrated in several studies that major improvements can be made in the external beam irradiation of prostate cancer by reducing safety margins using goldmarkers and strict positioning protocols. Using repeated recto-sigmoidoscopies as a golden standard we demonstrated that toxicity could be reduced even without IMRT, creating a possibility for improvement of the treatment also for those whose infrastructure is not suitable for IMRT. We also showed that even elderly patients want to be involved in the choice of type of therapy and are willing to take the consequences of this choice. Well known is our contribution to the treatment of rectal cancer. The surgeons made a major improvement in rectal cancer surgery and reduced the local control rate impressively. However, the TME-trial demonstrated that radiotherapy still has its role to play and preoperative radiotherapy is the treatment of choice. At present research is aiming at a refinement of the treatment approach. Hypoxia is the main topic for our translational research. In head and neck tumours it is easy to demonstrate how progress in radiotherapy has changed the role of other disciplines. Targeting hypoxia resulted in an important improvement in local control. Well known studies in this field serve as an example of research which moves from bench to bedside and back. The basic lessons of these investigations are now also being tested in other tumours eg. prostate and rectal cancer and in a new clinical trial in advanced cervical cancer in collaboration with our colleagues in Jakarta. The Dutch Bone Metastasis Trial and several side studies have contributed to our understanding of this frequent problem in cancer patients.

Improvements in oncology were also achieved by ESTRO's QA and educational programmes. The Committee on Education started in 1985 during the ECCO-meeting in Stockholm. A proposal was made for a system of modular teaching courses which started after the ESTRO meeting in Montecatini in 1990. In 2006 we had 16 teaching courses with over 1800 participants. These programmes have contributed to the harmonization of training in our profession and consequently to a general improvement in the quality of radiation oncology.