MONDAY 13 SEPTEMBER 1999

Teaching Lectures

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Cancer treatment – Major questions for the new millennium

J. Gordon McVie. *Cancer Research Campaign, United Kingdom*

The way we treat cancer patients in the next twenty years will be radically altered by the explosion in genetic technology. To a certain extent the questions will depend on how fast that technology gets into the pathology laboratories of our various hospitals around Europe but my personal list is the following -

- Based on genetic information from an individual patient's cancer, is anti-metastatic treatment required?
- If systemic treatment is indicated by the genetic makeup of the cancer, should it be given before local treatment or before and after?
- Which drug should be used in which sequence based on the genetic resistance profile?
- If local treatment is required, should it be surgery or radiotherapy?
- If radiotherapy is required as the local treatment of choice, what dose should be given, based on genetic read-out? And is there a requirement for radio-sensitisation, be it with a DNA repair blocker, oxygen source or vascular interference?
- Is there a need for follow-up/maintenance therapy based on genetic instability of primary or secondary tumours?
- What is the chance of second malignancy and how can we predict it?

A great deal is going to be expected of the pathology laboratories and the genetic specialists who will have to be trained to provide the basic genetic read-out on which the above questions will rest. However, a genetic revolution will have much greater impact than merely in treatment, for instance in identification of high-risk populations and early diagnostic tests, these topics were dealt with elsewhere.

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Paediatric tumours – What have we learnt? General messages for oncologists

H. Gadner. *St. Anna Kinderspital, Ärztlicher Direktor, Vienna, Austria*

Treatment of cancer in children and adolescents in the last 20–30 years has achieved remarkable progress. More than 70% of patients can be cured by modern strategies. There have been many important steps since the time when chances of survival were minimal to today's success. When considering this progress, several aspects should be mentioned: Cancer in childhood and adolescence is a rare disease with biological properties different from the majority of cancer forms in adulthood; remarkable progress was made in basic science allowing a better understanding of the diseases; this knowledge was tested through national and international clinical trials; therefore, for many years patients have been treated in highly specialised centres with interdisciplinary cooperation.

However, the dark side must be taken into account: Although we can cure 2/3 of paediatric cancer patients, the remaining third that we are still unable to cure with current strategies, remains the most difficult challenge for the future. Moreover, for families cancer is still traumatic, the diagnostic process is complicated, the therapy demanding and often life-threatening and the threat of relapse is constant! Also, the problems of long term sequelae are a matter of continuing concern.

By the year 2000, one person out of 900 in the population will be a long-term survivor of childhood cancer, many of whom will be suffering from late effects. Therefore, it is necessary to minimize this risk right now by tailoring treatment. Also, comprehensive follow-up care and supportive treatment, including social and psychological help need to be developed.

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The impact of biology on the practice of radiotherapy

N. James. *Queen Elizabeth Hospital, Medical School, Birmingham, United Kingdom*

Radiotherapy is the oldest and most frequently used non-surgical treatment for cancer and originated from the work of Roentgen, a physicist, over 100 years ago. Many major advances in RT, for example, megavoltage machines, computerised planning systems, stereotactic localisation and electron beam therapy, have been driven by the physics community not by biological research. The biggest biological contribution to radiotherapy is undoubtably fractionation around 70 years ago and the science of radiobiology has remained somewhat fixated on this area and its underlying dogma of the "4 Rs" of repair, repopulation, reoxygenation and reassortment. This has given rise to thais of therapies such as hyperbaric oxygen, radiosensitisers and more recently altered fractionation schedules such as CHART, probably the only therapeutically useful insight generated since fractionation by 70 years of mainstream radiobiology.

Most non-surgical cancer therapies are given in combinations, based on the insights of Goldie and Coldman on probability of drug resistance and cure, rather than at the maximal tolerated dose of a single agent. The use of drug combinations has resulted in striking advances such as CHOP for lymphoma and BEP for testicular tumours. Belatedly, combinations of radiotherapy with other anticancer therapies are now being actively explored and are resulting in striking improvements across a wide range of disease types, good examples being cancers of the anus and cervix. The potential interactions are complex and should result in cross-talk between the often relatively isolated radiobiology community and more mainstream drug development, which should yield new therapeutic opportunities. A further area of biological contribution to radiotherapy is in targeted therapy, for example, radioimmunotherapy; metabolically targeted treatments, from 131I to 89Sr and more recently boron neutron capture therapy. Other areas under investigation, but not yet impacting on clinical practice include prediction of radiosensitivity and gene therapy using radiosensitive promoters. The future impact of biology on radiotherapy is likely to grow and may help to move the field away from the hardware driven, dose escalation model that has dominated much of the last 50 years but which is inherently limited by biological diversity and in particular metastatic disease.

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Vascular endothelial growth factors and receptors involved in angiogenesis and lymphangiogenesis

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Angiogenesis, the formation of new blood vessels from preexisting ones, and the permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors Flt1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2). The Flt4 receptor tyrosine kinase is related to the VEGF receptors, but does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. Homozygous Flt4 knock-outs die after E9.5–10 due to failure of cardiovascular development. We have purified the Flt4 ligand, VEGF-C, and cloned its cDNA. While VEGF-C is homologous with other members of the VEGF/platelet derived growth factor family, it is made as a precursor protein having an extended N-terminus and a C-terminal half containing extra cysteine-rich motifs characteristic of a protein component of silk. VEGF-C is proteolytically processed, and binds and activates Flt4, which we rename as VEGFR-3. Transgenic mice expressing VEGF-C under a basal keratin promoter developed a hyperplastic lymphatic vessel network in the skin. However, proteolytically processed VEGF-C was also capable of stimulating VEGFR-2 and was weakly angiogenic. VEGF-C also induced vascular permeability, but its point mutant, which activated only VEGFR-3 did not. VEGF-D is closely related to VEGF-C, proteolytically processed and binds to the same re-

ceptors. Thus, VEGF-C appears to be an angiogenic and lymphangiogenic growth factor. Another related novel growth factor, VEGF-B was also cloned and found to be expressed in heart, muscles and less in other tissues. VEGF-B bound VEGFR-1, formed cell surface-associated, disulfide-linked homodimers and heterodimers with VEGF when coexpressed.

Tie, one of the receptor tyrosine kinases we have cloned, is expressed in mouse hematopoietic stem cell fractions and in all studied fetal endothelial cells. In transgenic mice the Tie gene promoter directs endothelial specific expression of heterologous genes. Tie was required during embryonic development for the sprouting and survival of new vessels, particularly in the regions undergoing angiogenic growth of capillaries. Our results thus demonstrate an increased complexity of signaling for endothelial cell proliferation, migration, differentiation and survival. Knowledge of these signals is essential for the control of angiogenesis in a variety of diseases including cancer.

[1] For a review, see: Korpelainen, E. and Alitalo, K.: Signaling angiogenesis and lymphangiogenesis. *Current Opinion in Cell Biology* 10: 159–164, 1998

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New imaging methods illuminating cellular structure and function

Rainer Pepperkok. *European Molecular Biology Laboratory, Meyerhofstrasse 1, 69012 Heidelberg, Germany*

The lecture will focus on methods to label and image cellular structures in living and fixed cells and organisms. The use of green fluorescent protein (GFP) tagged fusion proteins to study in living cells molecular dynamics, post-translational modifications and molecular interactions will be discussed. The basic concepts of the microscopy technology involved will be introduced and potential applications in high content/high throughput screening for the functional identification of novel genes from cDNA libraries will be shown.

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Rationale of the optimal interaction chemotherapy-radiotherapy

P. Lukas. *Universitätsklinik, Department of Radiotherapy, Innsbruck, Austria*

Over the last decades many potentially radiosensitizing drugs have been developed and an increasing number of trials succeeded to show a significant benefit of combined modality treatment.

However, still little is known about the optimization of treatment schedules for the combination of chemo- and radiotherapy, depending on the drug's mechanism of action. The dramatic expansion of knowledge regarding the molecular events that cause cancer and contribute to its fundamental biology could open new avenues for further treatment optimization. In an attempt to produce greater specificity of action and to take advantage of the latest discoveries in cancer biology, both commercial and academic investigators have turned their efforts toward specific molecular or biochemical targets known to play a role in cancer etiology and progression.

Such compounds, now entering clinical trial in large numbers, differ from traditional cytotoxic chemotherapeutic drugs in significant ways, but they represent at least potential tools to support traditional trials in a significant manner. Attention should now be directed toward the elaboration of combined chemo- and radiotherapy treatment schedules including these newly discovered entities that act at one of many new molecular targets, such as cellular and subcellular structures responsible for regulation of hypoxia, microcirculation, and in consequence affect drug delivery and action. Development of such schedules will likely require a new strategy for preclinical and clinical evaluation very different from that employed for traditional radio-chemotherapy alone.

In this teaching lecture the existing application schemes for combined drug- and radiotherapy will be discussed and some of the most promising models for optimization will be coined.

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Continuing medical education – The European agenda

J. Geraghty. *Professional Unit of Surgery, Nottingham City Hospital, Nottingham, United Kingdom*

There is now abundant evidence that variability in outcome in patients with cancer occurs. This factor is independent of tumour type as it has been demonstrated in many cancers including colon, ovarian and breast cancer as well as teratoma and is present in both their diagnosis and management. The well-established link between knowledge of health professionals and outcome has recently raised the profile of the need for these individuals to keep informed of advances in the medical sciences.

Although at present a professional obligation, the concept of continuing medical education is fast becoming a necessity in the routine of health professionals. They must now be able to demonstrate to their peers, politicians and most importantly their patients that they are up to date. To meet this need in oncology, he Federation of European Cancer Societies (FECS) has embarked on several initiatives over the last 2 years. It has, through its member societies, set up the Accreditation Council of Oncology in Europe (ACOE) whose remit is to develop a common accreditation system in Europe which recognises the multidisciplinary nature of cancer management. It will accredit courses in Europe and it is anticipated that its presence will facilitate recognition of credit points across European boundaries.

The long-term goal will be to facilitate freedom of movement of health professionals within Europe in their quest to obtain knowledge, which will be recognised at national level. This presentation will give an account of the history of this project as well as future prospects.