TUESDAY 14 SEPTEMBER 1999

# Teaching Lectures

489

## MDR – Proteins and their clinical relevance

H.M. Pinedo[1], J. Lankelma[1], G. Jansen[1], H.J. Broxterman[1]. [1]*Vrije Universiteit, Department of Medical Oncology, Amsterdam, Netherlands*

Drug transport proteins are expressed not only in tumor cells, but also abundantly in normal somatic cells, such as CD34-positive hematopoietic precursors, NK cells, dendritic cells and adrenal cortical cells (P-glycoprotein or Pgp), bronchial epithelial cells (MRP1) or hepatocytes (cMOAT or MRP2). These transporters are likely to primarily function as defense against natural occurring cytotoxins. The potential for differential modulation of drag toxicity in cancer treatment will depend on the relative expression levels of these proteins on tumor cells compared to the levels on normal cells.

It seems that the role of blocking Pgp to increase tumor cell sensitivity is modest in most if not all tumor types. Redistribution of drugs in the body by influencing transport across the blood brain barrier or in the liver by blocking Pgp is another therapeutic goal. Clinical studies with specific modulators of other transporters have not been reported yet.

In addition to the transport of exogenous cytotoxic compounds, a role of some of these transporters in the transport of certain physiological metabolites may be postulated. For instance, Pgp is suggested to transport as yet unknown molecule(s) supposed to regulate migration of dendritic cells. MRP1 may transport natural folates out of cells and MRP2 is a transporter for bile acids and also with low affinity for reduced glutathione. These examples illustrate that the role of drug transporters in normal physiology still remains largely to be investigated and may show new applications also in cancer therapy.

490

Abstract not received.

491

## Can we predict the efficacy and side effect of radiotherapy

J. Overgaard[1]. [1]*Aarhus University Hospital, Dept. Experimental Clinical Oncology, Aarhus, Denmark*

Radiotherapy is traditionally prescribed with a dose pending on the expected response and tolerance of the tumor and tissue in question, but not taking individual variations into consideration. In principle, therefore, no individual variation in sensitivity is expected in normal tissues and in tumors of a given type. On the other hand, clinical experience and basic biological knowledge have shown that there is a substantial clinical variation in the clinical response as well as cells and tissues in experimental situations are found to express a spectrum of individual radiosensitivity. As a consequence substantial research in the last decade has tried to derive predictive factors for individual radiosensitivity in tumors and normal tissues. This effort has, however, failed to identify new factors of major clinical relevance. In tumors factors related to intrinsic radiosensitivity, tumor cell proliferation and hypoxia have been investigated, but although such parameters are found to carry prognostic information the true predictive role of radiotherapy has not yet been substantiated, although it is likely that predictive information related to the importance of overall treatment time may emerge from knowledge of the degree of differentiation in certain tumors. With the exception of some rare genetic syndromes there is a similar lack of useful predictive factors related to normal tissue morbidity. More knowledge of the basic underlying mechanisms for radiosensitivity is emerging, but not clinically useful at present. Thus, the answer to the question addressed in the title is ānot yetā, but several important mechanisms have been identified which is likely to develop into useful clinical approaches. An overview of the past experience and perspectives for the future management of radiotherapy will be presented.

492

## What constitutes quality in breast cancer surgery

E.J.T. Rutgers[1]. [1]*Antoni van Leeuwenhoekhuis, Amsterdam, Netherlands*

The quality of the surgical procedure in a patient with breast cancer is not only restricted to an optimal technical act. The quality of the breast surgeon is reflected in many aspects of the management of the breast cancer patient.

– The diagnostic process: Before any surgical procedure is employed the surgeon should see after an optimal diagnostic process resulting in an estimation of the extent of the disease and the nature of the process followed by a properly designed treatment plan, discussed with the patient after multidisciplinairy discussion with radiologist and cytopathologist.

– The surgical procedure: An optimal surgical technique provides for the least possible mutilation with the best possible cosmetic result.

* the least possible complication rate
* the best possible cosmetique results
* conditions for the best locoregional control
* optimal information on the nature and extent of the disease locally and regionally. To obtain a high surgical standard proper training in breast surgery is mandatory, followed by protocolized surgical procedures in general practice and a sufficient caseload per surgeon. The most important determinant for high standard surgical cancer care is however a skilled surgeon, very much interested in and dedicated to breast cancer, working in the setting of a structured breast clinic (or withina breast team).

– Adjuvant treatment: The surgeon is the key to the information on local extent of the tumor (particularly in breast conservation) and regional – axillary – dissemination, which information dictates adjuvant treatment: radiotherapy and/or systemic therapy (SN-procedure!).

– Communication: Patients will only comply to and be satisfied by their treatment if they understand the nature of the disease, the background and impact of the treatment and have the possibility of a free choice between alternatives (after proper information). This requires from the surgeon time and communicative skills. Training with this respect is mandatory.

– Complications: The surgeon must be able to manage and recognize sequelae of the treatment: lymfedema, wound problems, cosmetic reconstruction (plastic surgery should be available), and psycological problems (the surgeon needs tools to recognize such problems and have support available).

– Breast Team: Quality control leading to high standard care is only guaranteed if breast cancer management is provided by a comprehensive team of specialists working in close cooperation. This team should at least consist of the surgeon, radiologist, pathologist, radiation oncologist, medical oncologist and breast care nurse.

493

## Is age a prognostic factor?

M.G. Mott. *Paediatric Oncology Unit, Department of Child Health, University of Bristol, United Kingdom*

Effective treatment is a pre-requisite for establishing prognostic factors and allows the selection of standard or experimental treatment on rational grounds. The effect of age on Leukaemia prognosis was apparent before curative treatment was developed and remains important with the present high cure rates. Specific genetic variants differ with age, e.g. the Philadelphia chromosome, t4;11 translocation, as does treatment tolerance, especially of bone marrow transplant procedures.

Embryonal tumours, e.g. neuroblastoma, show genetic variation with age, e.g., Triploidy, MYC N amplification, 1 p deletion, trkA expression, allowing prediction of cure in some young patients with surgery alone and spontaneous regression in others.

The high cure rate of nephroblastoma in young children decreases substantially in the rate adolescent/young adult patients. By contrast CNS Tumours do poorly in infants, partly due to reluctance to accept the severe toxicity associated with high dose radiation to the developing brain.

**Conclusion:** Intrinsic factors such as tumour genetics and normal tissue

tolerance to treatment vary with age and affect prognosis. Extrinsic factors such as patient (or parental) choice also vary with age and thus need to be taken into account when assessing crude survival rates with a particular treatment regimen.

494

## Computer-aided oncology: From basic research to clinical practice

J. Sgouros[1]. [1]*Imperial Cancer Research Fund, Computational Gerome Analysis, London, United Kingdom*

Since the announcement of the Human Genome Project in 1990, the advances in genome mapping and sequencing methods have led to an unprecedented increase in the amount of genomic information available. Indeed, as of today we have accessto more than 20 completely sequenced genomes from several species, including major pathogens and important model organisms. In addition, the new high-resolution map of the human genome contains more than 30,000 genes and the first working version of the human genome sequence is expected to be available in the spring of 2000. Furthermore, ongoing large-scale efforts are aimed at analysing the gene expression profiles of a variety of tumours at different stages. Besides generating new hypotheses about biochemical pathways that lead to malignancy and providing new potential targets for therapeutic intervention, such information can also form the basis for a detailed classification of tumours based on their molecular rather than morphological profiles.

The rapid advances in these areas are already changing the way we view and understand the cancer cell. The impact on diagnosis and therapy is already tangible and will be more dramatic in the near future. The genomic databases andassociated computational analysis tools on the Internet, initially aimed solely at the bench researcher, are already emerging as valuable resources for clinicians and counselling specialists. The lecture will provide an overview of these resources and their use, including case examples of applications to clinical oncology.

495

## Knock-out mice in cancer research

A. Berns, M. Vooijs, S. Marino, J. Jonkers, R. Meuwissen, J. Vink, H. Van der Gulden, P. Krimpenfort. *The Netherlands Cancer Institute, Division of Molecular Genetics, Amsterdam, Netherlands*

Gene inactivation studies are invaluable in assessing the function of oncogenes and tumor suppressor genes in development and malignant growth. However, detailed analysis of the role of tumor suppressor genes in these processes using the conventional knockout mouse models is often hampered by embryonic lethality or developmental aberrations. To circumvent these complicating factors associated with loss-of-tumor suppressor gene function we have generated a series of conditional tumor suppressor gene knockout mice. We have explored methods to switch the genes in a time-controlled and tissue specific fashion. Both transgenesis and somatic gene transfer was used to express Cre recombinase in the desired tissues. This technology permits us to induce specific tumors, to correlate specific genetic lesions with phenotypic characteristics, and hopefully to generate better models for testing intervention protocols. In addition, these mice are valuable source of cell lines that can be tested with respect to parameters that can be better studied in vitro such as growth, cell cycle regulation, response to irradiation, resistance to apoptosis, and genomic instability.

Some of the general points mentioned will be illustrated on the basis of studies performed with compound conditional mutants. Genes studied in various combinations include pRb, p53, Nf2, and p107. Inactivation was directed to specific tissues such as photoreceptor cells (IRBP-specific expression), Schwann cells, the intermediate lobe of the pituitary gland and the mesothelial lining of the thoracic cavity giving rise to an array of tumors such as primitive neuroectodermal tumors, pituitary tumors, choroid plexus tumors, and mesotheliomas.