Teaching Lectures

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Translational research in radiation oncology

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The goal of translational research is to facilitate the introduction of new diagnostics and therapeutics into the clinic from basic advances in technology and biology. For the field of radiation oncology, translation research is positioned well to capitalize on recent advances. In the past decade we have witnessed the complete sequencing of the human genome and an unprecedented increase in our basic understanding of cancer at the molecular level. This has stimulated the development of new drugs developed to target specific biological pathways. The combination of these drugs with radiotherapy has significant potential for improving anti-tumour responses over radiation treatment alone. This philosophy is based on the tenet that although new agents are often highly tumour specific and exhibit very good toxicity profiles, they are unable to kill the 9 to 10 logs of tumour cells required to cure a tumour. Thus, it is possible that promising new therapeutic compounds which could benefit standard therapies may be missed in poorly designed or single therapy trials.

Challenges for translational researchers in radiation oncology are twofold. The first is in making choices about which molecular pathways should be investigated as targets in the clinic. We have a wealth of information regarding genes, pathways, and responses which may be important determinants of therapy. The difficulty is in our ability to determine which of these pathways play important roles in which patients. In radiation oncology, there is a long history of attempting to understand the variables that contribute to failure and these include radiation resistance, proliferation and hypoxia. We now have a much better understanding of the genes and pathways which control these phenomenon and therapies targeting proteins in each of these pathways are being evaluated. Our success in combining new molecularly targeted therapies with radiotherapy in a rational and effective way is contingent upon our ability to identify those tumors which will benefit. Several recent examples suggest that genomic and/or proteomic profiles will allow such 'individualization' of therapy in the future.

The second challenge facing translational researchers is in the design of effective clinical trials which ensure a flow of information from the bedside back to the lab. With the realization that most trials will be negative coupled with the high costs of developing and testing new drugs, it is imperative that trials are designed with a goal to increase our basic understanding of disease. Historically, clinical trials have been the end-step on the development of a new therapy in which the primary goal was simply to determine if the new therapy was better than the old. This approach may have been logical in the past when the method of action of many drugs was poorly understood, but is much less useful today when speaking of drugs designed to target specific molecular pathways. One critical component of new trials is thus collection of biological tissue. In the case of a classical 'negative' trial, this tissue might be used to identify biological differences (genetic profiles) which identify a subset of patients who can benefit from the new treatment. Similarly, in the case of a 'positive' trial this tissue might be used to identify those patients who do not benefit and who would otherwise experience unnecessary toxicity. It is perhaps especially important to collect tissue in these more rare positive trials which may alter the future standard of care and thus prevent forever the possibility of identifying those individuals who don't benefit.

In this lecture I will highlight some of the recent developments in basic science which are stimulating translational research in radiation oncology and discuss their implications on the ways to carry out effective clinical trials.

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Proteomics in translational cancer research

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The sequencing of the human and other important genomes is only the beginning of the quest to understand the functionality of cells, tissues and organs both in health and disease. Together with advances in bioinformatics, this development has paved the way to the revolution in biology and medicine that we are experiencing today. We are rapidly moving from the study of single molecules to the analysis of complex biological systems, and the current explosion of emerging technologies within proteomics and functional genomics promises to elicit major advances in medicine in the near future.

In particular, proteomic technologies are expected to play a key role in the study and treatment of cancer as they provide invaluable resources to define and characterize regulatory and functional networks, investigate the precise molecular defect in diseased tissues and biological fluids, and for developing specific reagents to precisely pinpoint a particular disease or stage of a disease. For drug discovery, proteomics assist with powerful tools for identifying new clinically relevant drug targets, and provide functional insight for drug development.

Today, the application of novel technologies from proteomics and functional genomics to the study of diseases is slowly shifting to the analysis of clinically relevant samples such as fresh biopsy specimens and fluids, as the ultimate aim of translational research is to bring basic discoveries closer to the bedside. Here I will describe our efforts to apply proteomics and functional genomic approaches to the study of fresh tissue and tumour biopsies as well as fluids obtained from breast cancer patients. The working strategy is based on the analysis of samples obtained from the same patient, which are rapidly distributed to various members of DCTB, who apply various experimental paradigms. Members of DCTB have access to the data through a centralised database.

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Oesophageal and gastric cancer – classification and surgical consequences

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As far as the upper gastro-intestinal tract is concerned, the TNM-classification is focused on prognosis rather than on the therapeutic consequences. From a therapeutic point of view, tumors of the upper gastro-intestinal tract have to be differentiated into squamous cell tumors of the esophagus, on the one hand, and stomach tumors, on the other.

Problematic is the classification of tumors located at the gastro-esophageal junction. Whereas the therapeutic consequences for squamous cell cancer of the esophagus (always sub-total esphagectomy) or for gastric cancer (always total gastrectomy) are no longer truly controversial, adenocancer of the gastro-esophageal junction still requires careful discussion. There is no conflict, however, about regarding this to be a single tumor entity. Internationally there is also agreement about further sub-classifying the entity in three types ("... we have defined and described adenocarcinomas of the esophagogastric junction (AEG) as tumors that arise within 5 cm proximal or distal to the anatomical cardia. We have differentiated three distinct tumor entities within this area." Br J Surg 85: 1457-1459,1998). Type I corresponds in most cases to distal Barrett cancer of the esophagus and type III can be categorised just as reliably as cancer of the stomach. Regarding the cancerogenesis and treatment of type II, however, (true cardia cancer), there are two hypotheses: one is that it originates as "short Barrett esophagus", and the other that it is in fact gastric cancer. Our own analysis of 100 prospective cases has revealed that in about 30% of cases goblet cells could be detected, thus providing support for the short Barrett hypothesis, but in 70% of cases the oncogenesis corresponded to that common in gastric cancer.

This classification has now found international acceptance and widespread usage and has led to greater precision in the discussion of therapeutic consequences and also enabled the recruitment of comparable patient populations in studies. There is considerable agreement that the treatment for type I is a sub-total esophagectomy and that types II and III both require an extended gastrectomy. The implementation of modern reconstruction techniques now makes proximal gastrectomies feasible and the discussion concentrates on comparing them with total gastrectomies.

Modern classification of tumors of the upper gastro-esophageal tract that incorporates therapeutic consequences has to differentiate between squa-

mous cell cancer, genuine gastric cancer and the new entity, adenocancer of the gastro-esophageal junction (AEG).

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Cancer related anemia and its modification

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A number of recent studies have shown that anaemia is of greater importance for the quality of life of cancer patients than previously believed. Since erythropoietic agents are effective in increasing Hb levels in a majority of anaemic cancer patients, this has sparked an interest in cancer anaemia treatment.

Anaemia of chronic disease (ACD) is caused by several pathophysiologic mechanisms. A shortening of the red blood cell life span has long been known as well as a disturbance of iron metabolism, making iron accumulate in the reticuloendothelial system (RES) with reduced bioavailability to the erythroblasts. This has recently been given the name *functional iron deficiency*, a term defined as a state with presence of normal or elevated body iron stores but an iron deficient erythropoiesis. Patients with functional iron deficiency should be treated with intravenous iron. Recently an interesting role for the newly discovered iron regulating protein hepcidin has been suggested to explain this phenomenon. The last decade has also increased our knowledge about the effects of a number of cytokines as inhibitors both of Epo production and erythroblast proliferation.

The prevalence and incidence of cancer anaemia differ between tumour types as well as treatments. Gynaecological, haematological and lung cancer have the highest anaemia rates. Chemotherapy induces anaemia by depressing bone marrow activity, especially platinum-containing regimens. About 80% of patients with high risk tumour types will develop anaemia during chemotherapy.

Fatigue, the major symptom of anaemia, has been shown to be underestimated by health care providers, who give higher priority to symptoms with well-known therapies, like pain. The fatigue of anaemia has now been shown to be the problem that a majority of cancer patients find most debilitating. An active and focussed history-taking, also including changes in functional level, physically, socially and mentally, is essential to understanding the life situation of patients with anaemia.

The trigger level (last Hb before transfusion) for RBC transfusion is as low as 8.3 g/dl in Europe, indicating an unwarranted fear of transfusions. Epo treatment improves Hb in 60-70% of patients with cancer anaemia and has been shown to improve quality of life (QoL) in a large number of studies. The diversity in QoL-measurement methods makes Cochrane-type analysis unsuitable, but international and national recommendations, based on the QoL studies, now indicate a role for Epo treatment in symptomatic cancer anaemia. Importantly, a reduction of functional capacity should be regarded as a symptom, and the treatment goal should be a Hb level in the normal range or at least > 12 g /dl.

Recent review:

[1] Cella D, Dobrez D and Glaspy J. Control of cancer-related anemia with erythropoietic agents: a review of evidence for improved quality of life and clinical outcomes. Annals of Oncology 14:511-19; 2003.

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Targeting host-tumour interactions in myeloma therapies

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We have developed both in vitro systems and in vivo animal models to characterize mechanisms of MM cell homing to BM, as well as factors (MM cell-BM stromal cell interactions, cytokines, angiogenesis) promoting MM cell growth, survival, drug resistance, and migration in the BM milieu. These model systems have allowed for the development of several promising biologically-based therapies which can target the MM cell and the BM microenvironment (thalidomide/revamid, velcade, vascular endothelial growth factor receptor kinase inhibitor PTK787, histone deacetylase inhibitors SAHA and LAQ 824, 2 methoxyestradiol, and LPAAT inhibitor); those which target MM cells (telomestatin, heat shock protein 90 inhibitor 17 AAG, statins, insulin growth factor receptor inhibitor); and those which target only the BM microenvironment (IkB kinase inhibitors and p38MAPK inhibitors). It is our hypothesis that drugs in these classes will need to be combined to achieve complete eradication of MM cells, and we are presently studying their mechanisms of action at a gene and protein level in order to provide the framework for rational combination clinical trials to overcome drug resistance and improve patient outcome. Having demonstrated preclinical promise of these novel agents, we have rapidly translated our laboratory studies to phase I, II, and III clinical trials to evaluate their clinical utility and toxicity, and to move them rapidly from the bench to the bedside. Most excitingly, Velcade and Revamid have already demonstrated marked clinical anti-MM activity even in patients with refractory relapsed MM, confirming the utility of our preclinical models to identify and validate novel therapeutics. Importantly, gene array and proteomic studies have helped to identify in vivo mechanisms of action and drug resistance, as well as aiding in their clinical application. For example, gene microarray profiling of Velcade treated MM cells reveals induction of heat shock protein 90 stress response, providing the rationale for the combined clinical use of Velcade and 17AAG to enhance anti-MM activity. Study of proteomics also forms the basis for clinical application. For example, protein profiling of Velcade treated MM cells demonstrated cleavage of DNA repair enzymes, providing the rationale for combining Velcade with DNA damaging agents to enhance sensitivity or overcome resistance to these conventional therapies. Our studies have therefore demonstrated the critical role of host BM-tumor cell interactions both in MM pathogenesis and as targets for novel therapies. They have provided the framework for a new treatment paradigm targeting MM cell-host BM stromal cell interactions and their sequelae in the BM milieu to overcome drug resistance and improve patient outcome in MM.

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Immunotherapy of cancer - T-cell therapies

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This lecture aims to review the experimental basis and the state of T-cell based cancer immunotherapies in the clinics. During the last two decades the dogma of "non-immunogenicity" of spontaneous tumours has clearly been defeated by preclinical and clinical experiments. In particular through T. Boon's pioneering work it became obvious that spontaneous tumours in mouse and man carry tumour-associated antigens (TAA). Some TAAs under conditions such as specific vaccination can precipitate tumour rejection. Characterization of TAAs and vaccination studies in mouse and man subsequently defined the crucial importance of cellular immune responses for recognition of TAAs and destruction of tumours. T cells in cooperation with dendritic cells (DC) direct a complex cellular orchestra. T cells are unique among the other components involved in cellular immune responses. First, they can recognize endogenous peptides presented at the cell surface in context with MHCand represent the only external surveillance mechanism to control consequences of transformation-associated genetic alterations inside of a cancer cell. Secondly, T cells can generate immunologic memory, which is essential for cure. TAAs are either shared between many different cancer cells (sh TAA) or represent patient- specific individual antigens (indTAA). Most of the sh TAA are derived from normal gene products such as cancer-testis or tissue- restricted differentiation genes. Because T cell responses induced by such shTAA are limited by self- tolerance they mostly represent intermediate to poor candidates for rejection antigens. IndTAA are usually derived from mutated cancer genes, are recognized as foreign and represent efficient rejection antigens. Although at present multiple TAAs have entered the clinics their makings to more frequently precipitate rejection remains to be optimised. In parallel with our improved understanding of the molecular basis of T cell responses and their improved makings of TAAs three T cell based cancer immunotherapies have already entered the clinics. In early vaccination studies in advanced malignant disease a multiplicity of TAAs were applied in different formats with artificial or natural adjuvant such as DCs. Therapeutic responses and mild side effects were seen in a small minority of patients with different tumours. Donor lymphocyte infusions were successfully applied in the treatment of CML and AML patients relapsing after allogeneic stem cell transplantation. Adoptive transfer of tumour-specific T cell clones or more recently of patients T cells transduced with specific-specific T cell receptors have demonstrated preclinical efficacy and are presently developed in early trials. Although T cell based cancer immunotherapy is still in its infancy further rapid development and major patients benefits can be anticipated.

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The biology of paediatric cancer

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Molecular Biology of Childhood Cancers. The last decade has seen huge advances in the understanding of the biology of many childhood cancers.