MONDAY 22 OCTOBER 2001

Teaching Lectures

2

Molecular genetic epidemiology

Abstract not received.

3

Impact of pharmacogenomics on clinical practice

Abstract not received.

4

Modifying the effect of radiation through biology

G.D. Wilson. *Gray Laboratory Cancer Research Trust, Middlesex, United Kingdom*

Fractionation of radiotherapy has been the subject of much clinical research with schedules from as short as 12 days (CHART) to hyperfractionated or split-course therapy delivered over 8 to 10 weeks. Although there are differences in the clinical outcome between these schedules, these are not of great magnitude. The question to be answered is whether different subgroups of patients benefited from the different treatment schedules and whether underlying tumour biology determined the response to treatment. Proliferation characteristics should be a key component of the response to therapy but the failure of Tpot to consistently predict the outcome in conventional treatment schedules casts doubt on the current dogma that rapid tumour proliferation characteristics equate to poor outcome. Mammalian cells exist in either a state of proliferation or a state of quiescence. The fraction of cells actively proliferating determines the population's net proliferative rate. Critical controls of cell growth are located at two points during transit from quiescence to S-phase. Early events are activated during the first stage, termed 'competence' which is necessary to replenish specific mRNAs and proteins whilst regulated processes later in G1 constitute the'restriction point' necessary for successful progression into the cell cycle. Genes involved in these pathways are amongst the most frequently altered in cancer either by mutation, overexpression or loss of function. A scheme will be described which presents an alternative view of the inter-related pathways of proliferation, differentiation and cell death. It suggests that there is a cohort of slowly cycling cells within tumours, which may in fact be the key population as it is from these that both the rapidly cycling cells and those cells that will commit to differentiation, apoptosis and necrosis will originate. We need to consider the mechanisms of repopulation and whether deregulation of key genes facilitates recruitment or redistribution in response to treatment. Differences in the cell cycle control mechanisms between these different subpopulations within tumours may be exploitable for therapy.

5

Laparascopic surgery for cancer

Abstract not received.

6

Tumor invasion and metastasis

Nils Brünner. *Finsen Laboratory, Strandboulevarden 49, DK-2100 Copenhagen, Denmark*

Cancer progression is the result of several independent processes, including growth of the primary tumor, detachment of cancer cells from their original location, invasion of cancer cells through basement membranes into the surrounding tissue, access of cancer cells to blood and lymphatic vessels, adhesion to and invasion through the endothelium, allowing colonization at distant sites. In addition the cells in the tumor tissue direct a remodelling of the surrounding stroma, exemplified by neo-angiogenesis and desmoplasia. Extracellular proteases are either directly or indirectly involved in all of these processes.

In this context it has become evident that the stromal compartment of solid tumors plays an important biological role in tumor growth and metastasis, and several cellular localization studies have now shown that proteases, their receptors and/or inhibitors are predominantly expressed by the various non-epithelial stromal cells infiltrating the cancerous tissue.

In support of a biological role of stromal derived proteases are studies utilizing gene disrupted mice in which it has been demonstrated that host stromal cells paly a direct role for cancer growth and dissemination. Based on these observations, it has been suggested that the interaction between the tumor cells and the different non-malignant cell types with regard to proteases, their receptors and/or inhibitors within a tumor represents a concerted action which eventually leads to tumor progression.

It will be discussed during the session, how these experimental data can be used in the treatment and diagnosis of cancer.

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How to manage cancer in adolescence

H.F. Jürgens[1], L. Burns[1], S. Ahrens[1], P. Kaatsch[2]. [1] *UniversityChildren's Hospital, Dept. of Paediatric Haematology/Oncology, Münster, Germany;* [2] *University Hospital, Dept. of Medical Statistics and Documentaion, Children's Cancer Registry, Mainz, Germany*

The incidence of cancer in childhood and adolescence is well documented in population-based cancer registries and for children under 15 years approximates 14 new cases per 100,000 children per year. The incidence within the first five years of life is about twice as high as at later ages. Boys are more commonly affected than girls. Systemic malignancies are just as common as malignant solid tumours. The predominant systemic malignancy is childhood acute lymphoid leukaemia (approx. 30%), followed by AML (5%) and CML (0.5%). Non-Hodgkin lymphomas (7.5%) are more common than Hodgkin's disease (5%).

The most common solid tumours are in the CNS (>20%), predominantly astrocytomas, medulloblastomas/malignant central primitive neuroectodermal tumours, and ependymomas. The most common peripheral solid tumours are neuroblastomas (9%), nephroblastomas (7%), soft tissue sarcomas (7%, predominantly rhabdomyosarcomas), and bone tumours (5%, predominantly osteosarcomas and Ewing tumours), followed by germ cell tumours (3%), and retinoblastomas (2%). Carcinomas account for less than 1% of childhood malignancies. The distribution of diagnoses is significantly different between the first and second decades of life. All "blastomas" occur predominantly within the first five years of life and rarely thereafter. Acute lymphoblastic leukaemias have a peak incidence in pre-school age, and later reach a plateau. The lymphomas increase in incidence with age and rarely occur below five years of age. Bone tumours predominantly occur in the second decade of life whereas rhabdomyosarcomas and germ cell tumors show a biphasic incidence.

The therapeutic tools in childhood malignancies include chemotherapy as well as radiotherapy and surgery where applicable. The global 5-year survival is 76%, ranging from approx. 60% for most sarcomas to 80-90% for leukaemias and lymphomas (ALL 84%; AML 48%) to approx. 90% for nephroblastomas and germ cell tumours.

Despite impressive survival and cure rates the impact of such intense treatment on patients and families is high, and late sequelae including infertility, compromised cardiac and renal function, and the induction of second malignant neoplasms (approx. 5% after 20 years) are significant.