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.

The initial advances were made in identifying genes that predispose to a greatly increased risk of childhood cancer. Such genes included RB, WT1 and p53. These illustrate the varied contribution of somatic mutation of predisposition genes to specific childhood cancers. Mutation in the RB1 gene seems to account for nearly all cases of retinoblastoma with heritable mutations occurring in approximately 40% and tumour specific defects in the remaining allele found in nearly all. By contrast, heritable mutations in WT1 occur in less than 5% of children with Wilms tumour and somatic mutations occur in only a further 10-20% of tumours. Mutation of the p53 gene, which underlies the Li Fraumeni syndrome, is very common as a somatic event in many adult tumours. However, this is not the case in childhood cancer, where somatic p53 mutations are unusual except in certain subtypes such as anaplastic Wilms tumour and some sarcomas.

Analogous to leukaemias, several childhood solid tumours have been shown to carry balanced chromosomal translocations resulting in fusion genes and chimeric proteins with novel, oncogenic properties. Examples include the EWS-FLI1 fusion in Ewing family tumours and the PAX3/7-FKHR fusion characteristic of alveolar rhabdomyosarcoma. Development of molecular methods to detect these fusion genes has led to a new era of molecular diagnostic pathology and also clinical research on the significance of micro-metastases and minimal residual disease. Mutation of the INI1 gene in rhabdoid tumours illustrates their common biology despite their varying anatomical sites. INI1 is an important component of chromatin remodelling complexes, suggesting a target for therapeutic intervention.

The study of the molecular biology of childhood cancers continues to bring broader insights into the biological control mechanisms of cellular proliferation and differentiation. Ultimately this should point the way towards novel therapeutic strategies.

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The status of bone marrow transplant clinical trials

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The purpose of this teaching letter is introduction of the ongoing trials related to EBMT STWP. Currently, EBMT STWP has 7 prospective studies. These studies: 1) HIDOC European intergroup study that is a randomized phase III trial of sequential HDC or conventional chemotherapy (CC) for advanced ovarian cancer in the de novo setting. J. Ledermann, from London, is conducting this trial. To date, 136 patients have been accrued. 2) Randomized phase III trial of HDC with ASCT versus CC in platinum sensitive relapsed ovarian cancer. This study is being conducted by T. Demirer, from Ankara and started to accrual in the beginning of 2003. 3) Phase III randomized trial of sequential HDC versus CC for the treatment of small cell lung cancer. S. Leyvraz from Lausanne is conducting the study. To date, 114 patients have been accrued. 4) Phase I study of allogeneic stem cell transplantation with reduced conditioning for the treatment of the patients with advanced solid tumors. D. Niederwieser from Leiden is conducting this study. This is a hot topic in the field of transplantation and oncology in recent years. Therefore, study has a fast accrual rate compared to the other ongoing studies. Until now, 36 patients from 12 transplant centers have been reported. The vast majority of the patients were treated from renal cell carcinoma (RCC) (n=22) and for breast carcinoma (n=7) and remaining 7 patients were treated for other diseases. Of 36 patients, 19 received cyclophosphamide (Cy), fludarabine (Flu) and ATG, 10 patients received thiotepa, Cy and Flu and 4 received 200 cGy-TBI and Flu as conditioning regimen. This interim report shows that RCC is the most frequent indication and Cy Flu ATG is the most frequent conditioning used in this study. For patients with renal and breast cancer, the trial will be closed probably by the end of 2003. We'll start to phase II randomized studies by the end of this year. 5) A phase II study of intra-familial allogeneic stem cell transplantation for patients suffering from metastatic RCC, which is a joint protocol of the EBMT STWP and French national group. D. Blaise from Marseille will conduct this study and it will be launched soon. 170 patients will be accrued, 60 in transplant group and 110 in control group. 6) A phase III randomized clinical trial for metastatic breast cancer patients achieving complete response to CC. This study will start this year and be conducted by Drs. N. Ueno and G. Hortobagyi from MDACC in Texas. 7) Same as study 6, a randomized trial for metastatic breast cancer patients achieving partial response to CC will be started soon. This will be conducted by M. Aglietta from Turin and will be a joint protocol of EBMT STWP and Italian GITMO Group. We believe that introduction of current ongoing EBMT studies to medical oncology society will increase the cooperation between oncologists and transplanters on the way to have fast answer whether HDC can be a tool for the treatment of some solid tumor.