Symposia

917

Anti-HER2 monoclonal antibodies

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Breast carcinomas express high levels of ErbB receptors, such as the EGF (ErbB1) receptor and the closely related HER2 (ErbB2) receptor, and their overexpression is associated with a more agressive clinical behaviour. Monoclonal antibodies, tyrosine kinase inhibitors and other ErbB receptor targeted approaches can inhibit breast cancer growth and have moved to the clinic. The single agent clinical trials with trastuzumab, a monoclonal antibody that targets HER2, provided proof-of-concept of the activity of growth factor receptor targeting for the treatment of breast cancer. Furthermore, trastuzumab prolonged overall survival, the most important and elusive goal in metastatic breast cancer, in patients treated initially with trastuzumab and chemotherapy compared with patients treated with chemotherapy alone. Recently, a series of clinical trials have further enhanced our knowledge on how to maximize the clinical use of trastuzumab: only tumors with high level of HER2 overexpression as determined by immunohistochemistry (HER2 3+) or gene amplification appear to benefit from trastuzumab therapy; the activity of single agent trastuzumab in the first line setting is excellent and at least as high as any conventional chemotherapy agent in HER2 positive patients; a series of well tolerated and active combinations of chemotherapy and trastuzumab are emerging. In particular weekly taxane + trastuzumab and weekly vinorelbine + trastuzumab fulfill these requimements; a new q 3 week dosing schedule may become available in the future if ongoing studies confirm similar efficacy to the q week regimen. Available data suggests an optimal pharmacokinetic profile taking in consideration its very prolonged half-life; and finally and most important, adjuvant studies with trastuzumab are currently underway both in the United States (NSABP-B31, Intergroup study) and in Europe (HERA trial and BCIRG). Another anti-HER2 antibody, designated 2C4, might be active in cases of not dramatic HER2 overexpression where HER2 may act as a very potent heterodimer partner of other ErbB receptor family members. Novel antibody-based molecules such as intracellular antibodies, bispecific antibodies, and antireceptor antibody fusion molecules are also entering clinical trials.

918

Monoclonal antibodies anti-angiogenesis

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The use of inhibitors of angiogenesis has been the focus of the development of a number of novel therapies. While small molecule inhibitors of angiogenesis have focused on specific targets such as the tyrosine kinase pathway for vascular endothelial growth factor, this has the disadvantage of not inhibiting both of the receptors for VEGF signaling. In contrast, antibodies that block the activity of VEGF can inhibit signaling through all relevant receptors. Two monoclonal antibodies have been developed as specific inhibitors of VEGF-induced angiogenesis. rHuMAbVEGF is a IgG antibody which inhibits all isoforms of VEGF. Phase I trials have demonstrated safety of the molecule through doses of 10 mg/kg both alone and in combination with chemotherapy. Minimal evidence of anti-tumor activity defined by minor responses and disease stabilization were seen. Subsequent phase II studies in combination with chemotherapy have been conducted in patients with non-small cell lung cancer colorectal cancer. Adverse events seen in these studies have included a higher than expected rate of thromboembolic events as well as an apparent increased risk of tumor bleeding for a specific subpopulation of lung cancer patients. In both studies, an apparent improvement in either response rates of progression-free survival compared to randomized placebo controls was seen though the sample sizes were inadequate to make these differences statistically significant with adequate power to accept the benefit as real. As a result, subsequent phase III randomized, placebo-controlled trials are planned or ongoing. Single agent studies in patients with refractory cancer have also been conducted, specifically in breast cnacer and prostate cancer. The preliminary results of the breast cancer trial was presented previously and demonstrated a propensity for the development of hypertension in ~25% of the patients treated. Objective responses to single agent therapy were seen, indicating that there may be a role for primary anti-angiogenic therapy in patients with specific refractory cancer. The second humanized antibody, HuMC833 is an IgG4k for which the phase I trial incorporating imaging and biopsy was recently reported. This phase I trial importantly demonstrated the variability of anti-angiogenic response to therapy as measured by PET flow scans both within the same as well as different tumors. This highlights the importance of developing surrogate markers for the activity in clinical therapy.

919

Antibody blockade of the epidermal growth factor receptor combined with radiation

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The Epidermal Growth Factor Receptor (EGFR) has emerged as a key molecular target for modulation in cancer therapeutics. Epithelial tumors comprise approximately two-thirds of all human cancer and a correlation between overexpression of EGFR and clinically aggressive malignant disease has been established for many cancers. The initial rationale underlying EGFR signal interruption as an anti-cancer strategy involved proliferative growth inhibition. However, more recent studies now confirm the capacity of EGFR down-regulation to modify cellular radiosensitivity, chemosensitivity, apoptosis, invasion capacity, angiogenesis and DNA damage repair. The favorable interaction profile for EGFR blocking agents combined with radiation and/or selected chemotherapy drugs has stimulated clinical trials in diverse anatomic sites including head and neck, colorectal, pancreatic and lung. Monoclonal antibodies (mAbs) directed against the EGFR show great promise in preclinical and early clinical trial results for a spectrum of epithelial tumors. The most mature development to date for EGFR mAbs is that of C225 which is a chimeric mAb to the EGFR. A fully humanized mAb to the EGFR has also been developed (ABX-EGF), and a mAb directed against the most commonly expressed mutant form of the EGFR (EGFRvIII) in human tumors has been established (mAb 806). Preliminary results and current development status for these agents are reviewed. The spectrum of cellular and biological effects which follow molecular blockade of the EGFR is enlarging, and reflect the central role of this receptor in regulating epithelial cell behavior. Potential advantages and disadvantages of accomplishing EGFR blockade using the mAb approach compared with the use of tyrosine kinase inhibitors are previewed. Molecular inhibition of EGFR signaling in combination with radiation or chemotherapy represents a highly promising investigational arena. An update regarding current translational research efforts and early clinical trials is provided.

920

Monoclonal antibodies for therapy of solid tumors

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The therapeutic potential of monoclonal antibodies for cancer became soon evident after the original description of the hybridoma technique in 1975. Nevertheless, it took almost two decades of inconclusive clinical trials before more consistent positive treatment effects were reported. Several explanations for these impressive failures have been discussed, among them inaccessibility of antigenic cells within solid tumor tissue, inadequate target structures, cellular heterogeneity due to genomic instability, immunogenicity of the antibody – to name a few. The nature of the targets, – be it a growth factor receptor or an adhesion molecule –, as well as "humanization" of the effector portion of the antibody both seem to play a critical rôle for therapeutic efficacy. My review will focus on recent results of antibody trials showing efficacy in combination with defined chemotherapeutic agents. Recently, also novel antibody formats such as single-chain bispecifics are

being tested in clinical trials. Their perspectives will be discussed as well as the targeting of antibodies to minimal residual cancer cells in order to preempt metastasis formation.

921

Clinical epidemiology

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A useful new concept is if clinical epidemiology would be recognised as the basic methodological tool for clinical cancer studies. The reasons are several:

1) Clinical epidemiology can be defined as the methodological arsenal for study of illness related outcomes in persons who have sought advice in the health care system. Epidemiology investigating causes of cancer has long grappled with problems in design and biostatistical analyses of studies done under difficult circumstances. The field has benefited methodologically and we can import these improvements to clinical studies as many of the basic problems (e.g. estimating risks, rates, relative and absolute effects of interventions etc) are the same. 2) Only in randomised clinical trials (RCT) and meta-analyses (MA) have we so far taken up the challenge, but both RCTs and MAs can improve even more. 3) Not everything can be studied by RCTs and methodologically sound designs are needed in such settings. Examples are studies of unintended effects of treatment and of prognostic markers. Today, many non-randomised cancer clinical studies do not make full use of their data due to unsuitable design and limited analytical scope. 4) In non-randomised clinical studies of intended effects of treatment, problems with bias are even larger than in other observational studies. All methodological lessons learnt from epidemiology are needed. 5) For some cancer diagnoses there exist large clinical databases, which however are little utilised. Well designed studies within those can be valuable for several purposes. 6) Research in diagnostic strategies need methodological improvement, correct diagnosis and early detection being key issues in cancer. 7) Studies in cancer forms with long survival entail problems such as effect modification from comorbidity and competing causes of death, which need to be analysed properly.

922

Epidemiology in health policy

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Ideally, all of a society's activities should be assessed and particularly those carried out at the cost of the general public. Cancer prevention and control are not exceptions to this rule. Good, routine statistical back-up is very useful and can be supplemented by special studies. Experience from other countries is not necessarily always applicable or cannot always be repeated. Each country should thus make its own efforts for planning and evaluation.

The basic measure for health policy in cancer is the evaluation of the occurrence of cancer. The indicators incidence, prevalence and mortality can be used for various purposes in policy making. For planning and evaluation of health policy actions, predictions play a central role. Making reliable predictions for the occurrence of cancer is particularly challenging as the risk factors and their distributions and effects in a population are not precisely known for most cancers. Population-based survival rates provide a rough quality control of cancer care in a population. Unexpected differences have lead to studies elucidating the background of the findings.

A population-based cancer registry is an important instrument in this activity. It does not only provide the necessary numerical background but can also provide material for a variety of epidemiological studies of cancer aetiology and evaluation of interventions, provided that an adequate legal basis and sufficient resources exist. Under these conditions important economic savings may be achieved, both in the assessment and in the targets of assessment.

923

Low penetrance susceptibility genes for breast cancer

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Mutations in BRCA1 and 2 account for about 15–20% of familial clustering of breast cancer. The number and type of genes that account for the remainder, is not clear. It is however plausible that at least some of this genetic predisposition is attributable to the effects of multiple, common, but individually weak genes.

The prospect of a polygenic approach to common disease, in which genotypic profiles are used to stratify individuals at different levels of risk, has raised much enthusiasm for its potential in targetting screening and prevention. Others are more sceptical, believing the size of genetic effects, compared with chance and environment, to be too small to be of practical use.

We have used a large population-based series of breast cancer cases to model the distribution of genetic risk in the population. The most plausible model gives a log-normal multiplicativity. The difference in risk between the lowest and highest quintiles is 40-fold. We conclude that genotype profiles are likely to be of use, and to provide more information than 'established' clinical risk factors.

To build a profile, one must identify the genes. Using association studies with snps in a large series of breast cancer cases and controls, we have identified 6 tentative positive associations in 29 candidate genes. The interpretation of these results will be discussed.

924

Food consumption patterns, energy balance and cancer risk

Abstract not received.

925

Impact of advanced technology in cancer of the head and neck

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Introduction: This paper discusses the merits of advanced technology; 3 clinical examples are taken from our own department. First, the evolution in intraoperative brachytherapy (IOBT). Secondly, Stereotactic Radiation Therapy (SRT) with modified frames, and thirdly the sparing potential of external beam Intensity Modulated Radiotherapy (IMRT) techniques.

Material & Methods: We routinely implant cancers of the base of tongue; the dosimetry of this volume implant is time consuming, due to the need for catheter identification on X-ray films. For that reason our protocol does not permit IOBT in volume implants. A solution was presented by CT-based automatic catheter recognition. An additional innovation is the introduction of inverse planning, making BT now a real 3DCRT/IMRT treatment option. The 2nd clinical example is SRT for boosting the primary. Recently the TLC/GTC-frame (Radionics), was modified in our institute to eliminate the problem of not being able to use SRT frames because of severe mucositis. Thirdly, the sparing potential of IMRT using dMLC or step and shoot techniques, will be illustrated (large fields and boost combined). For 3DCRT/IMRT in general, we developed a 3-D target definition of the neck. We are now working on similar guidelines for various primary sites.

Results and Discussion: All 3 clinical examples demonstrate advancement in technology being beneficial to the treatment of H & N cancer patients. However, a price is to be paid. First we will show cost computations for an exemplified tumor (T2bN2 Nasopharynx), treated in our center as of 1996 by neoadjuvant chemotherapy (CHT) in combination with conventional external RT (70 Gy), and brachytherapy (11 Gy). As of 2001, this patient will be treated by neoadjuvant CHT, IMRT 70 Gy and SRT (11.2 Gy), however, with a significant increase in total costs. Secondly, the departments of Radiation-Oncology in The Netherlands have on average a waiting time (WT) of 4–6 wks. The increasing effort in implementing advanced technology in the clinic, given also the shortage of highly skilled personnel, can lead to an increase in the WT and therefore to a less favourable situation. In fact,