Thursday 21 November

PLENARY SESSION 4

Therapy prevention interface

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Interface of treatment and prevention research

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Abstract not received.

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Chemotherapy and chemoprevention: two currencies or two sides of the same coin?

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The dramatic improvement in our understanding of cancer biology which has occurred over the last two decades has undoubtedly impacted on the development of new cancer chemopreventive agents. A number of putative chemopreventives, e.g. resveratrol, genistein and celecoxib, exert their efficacy via interference with biochemical processess germane to tumour promotion/progression, such as mitogenic signalling, activities of cyclooxygenase-2 (COX-2) and kinase enzymes or hormone-dependent cell survival. The agents currently in development have not been rationally designed. Instead the suspicion that they may prevent cancer has been raised by serendipitous or epidemiological observations. A pivotal difference in agent development between chemotherapy and chemoprevention is the absolute requirement for lack of toxicity in the case of chemopreventives. Many agents possess a multitude of mechanisms of action, and diet-derived substances may exert their beneficial effect only when they are present in the authentic food matrix. In the face of this complexity, the rational preclinical and clinical development of putative chemopreventive agents needs to use pharmacokinetic and pharmacodynamic paradigms which are employed in the contemporary development of novel chemotherapeutic agents. Curcumin serves as an instructive example. Its ability to downregulate the expression of COX-2 in cells renders it a potential alternative to chemopreventive NSAIDs. We elucidated the pharmacokinetic and pharmacodynamic parameters which determine the efficacy of curcumin in the Min/+ mouse. The Min/+ mouse is a model of human FAP, which is caused by a mutation in the Apc gene. We and others found that the systemic availability of curcumin in rodents and humans is poor, related to its avid metabolic conjugation and reduction. The ability of curcumin to reduce adenoma multiplicity in Min/+ mice was accompanied by downregulation in the target tissue of COX-2 expression and of levels of DNA adducts which reflect endogenous oxidants. The gastrointestinal mucosal level of curcumin required for efficacy was just above 100 nmol/g tissue, and the efficacious dose (0.2% in the diet) translates into a daily dose in humans of ~1.6 g. We are currently testing the hypothesis that efficacious target tissue levels can be achieved in humans who consume curcumin capsules. In the framework of novel agent development, chemoprevention and chemotherapy are two sides of the same coin.

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Progress in chemoprevention of breast cancer

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Results from primary prevention trials have shown that tamoxifen lowers breast cancer incidence in at-risk subjects. As follow-up continues, and more events are observed, the initial differences between the P1 trial and two European trials has become less evident. Moreover, the results of the IBIS trial have confirmed the efficacy of tamoxifen in women with strong family history. Finally, raloxifene was shown to reduce breast cancer in an osteoporosis trial. Based on these findings, and because of the estrogenic adverse events of tamoxifen at endometrial level and of both SERMs at vascular level, new strategies are currently being pursued to improve the risk benefit ratio of chemoprevention intervention. First, it is evident from the three tamoxifen trials where HRT was allowed that the combination of HRT and tamoxifen can reduce risks while retaining benefits of either agent for all of the three major endpoints (breast cancer, endometrial cancer and VTE). The H.O.T. study (HRT Opposed by Tamoxifen)is addressing this issue in a phase-3 trial. Second, the search for the most appropriate dose of tamoxifen is an important area of research as recent data indicate that a dose reduction can retain drug's antiproliferative effect on breast cancer while reducing the estrogenic effects on different target systems. Third, new SERMs are being searched which can minimize the agonistic effects of tamoxifen, and the STAR trial is assessing the efficacy and safety of tamoxifen and raloxifene in a large trial. Fourth, the new third generation aromatase inhibitors (AIs) have shown good efficacy in advanced breast cancer and in the adjuvant setting with an acceptable toxicity profile. A trial of anastrozole in 6,000 postmenopausal women who are at increased risk for breast cancer will soon be conducted (IBIS-II). Finally, control of ER negative breast cancer is a priority as approximately one third of all invasive cancers are ER negative. New agents are being evaluated in women at increased risk for ER negative breast cancer. These include inhibitors of tyrosine kinase, cyclin dependent kinase inhibitors, PPARgamma ligands (glitazones), RXR selective ligands (rexinoids), COX-2 selective inhibitors, demethylating agents, histone deacetilase inhibitors and Vit D3 derivatives. Morphological and molecular biomarkers are used to select candidates at higher short-term risk and to assess the response to agents in phase II prevention trials.

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Surrogate endpoint biomarkers in chemopreventive agent development

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Molecular surrogate endpoints will be critical for translational studies of the rapidly increasing number of developmental molecular-targeting preventive agents. Two models, retinoids in head and neck carcinogenesis and nonsteroidal anti-inflammatory drugs (NSAIDs) in colorectal carcinogenesis, contribute substantially to chemopreventive molecular study. Retinoid/head and neck studies provided the initial proof of principle of cancer chemoprevention and a pioneering translational paradigm of multistep carcinogenesis and chemopreventive-agent mechanisms. A major mechanism of cancer delay appears to involve detouring multistep carcinogenesis down alternative pathways. Well illustrated by translational studies in head and neck cancer prevention, this detour concept is highly relevant to preventive molecular-targeting approaches. Altered genes, such as p16 (on 9p), p53 (on 17p) and cyclin D1 (on 11q), are associated with head and neck cancer development and represent potential molecular targets and detours for cancer prevention. Several agents may reverse the effects of these genetic alterations and divert carcinogenesis down alternate pathways. Recent clinical and translational studies of a retinoic acid-based preventive regimen in the head and neck illustrate a molecular detour at 11q13 involving cyclin D1, which is increased and dysregulated in advanced head and neck IEN. The regimen suppressed cyclin D1 expression (likely via retinoic-acid-receptor-mediated proteolysis), and this suppression correlated with cancer delay. It may be possible to enhance cancer delay through combinations of molecular-targeting agents (e.g., NSAIDs plus retinoic acid) that produce detours at multiple critical molecular junctures within multistep carcinogenesis. Seminal contributions of the NSAIDs/colorectal model to preventive molecular-targeting strategies include the FDA approval of celecoxib in FAP and identification of many promising molecular targets, such as lipoxygenases (LOXs), peroxisome proliferator-activated receptors, PKC, NFkB, and cGMP, for chemopreventive drug development. Recent study of polyunsaturated fatty acid metabolism in the NSAID colorectal model has identified a dynamic cyclooxygenase-LOX balance and produced the novel concept of LOX modulation to arrest, reverse or delay carcinogenesis. Exciting advances in target-tissue sampling and imaging promise to play an important role in advancing molecular targeting chemopreventive study.