S24. Chemoprevention of Colorectal Cancer: Ready for Routine Use?

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At the dawn of this century, cancer prevention is the new frontier for cancer therapy. This is especially significant because cancer is predicted to become the leading cause of death, surpassing heart disease, by the end of this decade. Colorectal cancer (CRC) is a major health concern, with more than 1,000,000 new cases and 500,000 deaths expected in 2004. Science and technology have evolved to a point where we are able to use our knowledge of cancer biology to identify individuals at risk and interrupt the process of malignant transformation at the level of the pre-cancerous lesion. Recent progress in molecular biology and pharmacology increases the likelihood that cancer prevention will increasingly rely on chemoprevention. Chemoprevention, a new emerging science, means the use of agents to inhibit, delay or reverse carcinogenesis. Recent observations suggest a number of potential targets for chemoprevention. Many agents including folic acid, calcium, estrogen, vitamins, olpitraz, ursodiol and fiber have shown a great deal of promise, but only modest chemopreventive efficacy in clinical trials. There is much evidence suggesting a link between aspirin or NSAIDs consumption and CRC prevention, as supported by results from 100 animal studies and 35 epidemiological studies, 32 of which demonstrated a reduction of CRC incidence in patients regularly taking NSAIDs. However, NSAIDs consumption is not problem-free, as figures from 1997 showe 107,000 hospitalisations and 16 500 deaths due to NSAIDs consumption in the US alone, equalling the mortality from AIDS or leukaemia. Therefore, although chemoprevention of CRC is already possible, drugs that have more acceptable side-effect profiles than the currently available NSAIDs are required. COX-2-specific inhibitors, which have an improved safety profile, as compared to traditional NSAIDs that inhibit both the COX-1 and COX-2 enzymes, are an ideal drug candidate for the prevention or treatment of cancer for several reasons. The link between COX-2-specific inhibitors and carcinogenesis is now well established. Celecoxib (Celebrex, Pfizer, NY, USA) was shown to inhibit the growth of many cancer cell lines. In my lab celecoxib was shown to be 3-4 times more efficient in inhibiting the growth of transformed cells than the growth of normal cells. This growth inhibition was associated with induction of apoptosis through the caspase pathway. It is of interest that rofecoxib (Vioxx, Merck, NJ, USA) does not inhibit cell growth in vitro, but is a potent drug in vivo. In COX-2 knockout mice that have been crossed with Min mice, the progeny have demonstrated a marked reduction in the number of intestinal tumours. Celecoxib has chemopreventive activity in the azoxymethane (AOM) rat model, and is very effective when administered during the promotion/progression stage of colon carcinogenesis. In humans, up to 50% of polyps and 85% of colonic tumours over-express COX-2. In a recently conducted double blind, placebo-controlled clinical study, subjects with familial adenomatous polyposis (FAP) received celecoxib (400 mg bid) for 6 months. Celecoxib was well tolerated and effective in the treatment group. Patients treated with celecoxib had a 28% reduction in polyp number and 30% reduction in polyp burden, as compared with patients who received placebo. International multi-center trials are currently underway to evaluate the efficacy of celecoxib and rofecoxib in the secondary prevention of colorectal polyps. A primary objective of current human studies is to determine whether a selective COX-2 inhibitor induces regression of pre-malignant lesions. Promising pre-clinical findings and the encouraging results of the FAP study have stimulated several others clinical trials utilising selective COX-2 inhibitors. Given the frequent need for surgical intervention in these pathologies, identifying a pharmacological approach to achieve either regression or stabilization of disease would be a major significant clinical advance. International multi-center trials are also currently underway to evaluate the efficacy of celecoxib in the secondary prevention of other pre-malignant lesions such as Barrett's oesophagus, aktinic keratosis, superficial bladder cancer and oral leukoplakia. Inhibiting the growth of pre-cancerous and cancerous cells without affecting normal cells is generally the ultimate aim of cancer treatment, but is of particular importance in chemoprevention studies, which may be long term in nature, involve healthy subjects at the outset and have strict adverse-event requirements. Cancer prevention is certain to be a significant focus of research and intervention in

the coming years, propelled by the realization that we will be able to identify both individuals susceptible to specific cancers as well as the molecular targets that can alter or stop the carcinogenesis process. Pharmacology and genetics are collaborating to develop new chemoprevention agents designed to affect molecular targets linked to specific pre-malignant or predisposing conditions. However, the value of such prophylactic strategies has yet to be confirmed in the current ongoing randomised, double blind, placebo controlled studies. The ultimate drug may be a specific COX-2 inhibitor that offers the benefits of protection against cancer, without the gastrointestinal side effects associated with traditional NSAIDs.