Colorectal cancer chemoprevention: Ready for practice?

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Introduction

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 worldwide in 2009 [1]. In the United States (US), CRC affects nearly 150,000 people each year with an estimated 49,960 deaths from CRC expected to occur in 2008, accounting for 9% of all cancer deaths. Mortality rates from CRC have been decreasing in both men and women over the past two decades with a steeper decline in the most recent time period (1.8% per year from 1985–2002 compared to 4.7% from 2002–2004). This decrease reflects declining incidence rates and improvements in early detection and treatment [2]. Nevertheless, CRC death rates remain unacceptably high, calling for better compliance with screening guidelines and the identification of complementary strategies to reduce the burden of this deadly disease. CRC has a natural history of transition from precursor to malignant lesion that spans, on average, over 15–20 years, providing a window of opportunity for effective intervention and prevention. CRC meets the criteria of a disease suitable for chemopreventive intervention by being one that is prevalent as well as associated with considerable mortality and morbidity rates. Indeed, chemoprevention is an emerging science that offers a promising approach for reducing mortality from CRC.

Chemoprevention involves the long-term use of a variety of oral agents that can delay, prevent or even reverse the development of adenomas in the colon, as well as the progression from adenoma to carcinoma. Recent observations suggest a number of potential targets for chemoprevention.

Many agents including curcumin, selenium, calcium, oestrogen, olpitraz, ursodiol, polyphenols, statins and fibres have shown a great deal of promise, but only modest chemopreventive efficacy in clinical trials. These agents can be broadly classified into three categories based on their mechanism/s of action [3]:

(1) Anti-inflammatory modulators including cyclooxygenase (COX)-2, EP 1-4, and nuclear factor (NF)-kB.
(2) Signal transduction modulators including epidermal growth factor (EGF), insulin-like growth factor (IGF) receptor inhibitors, anti-vascular endothelial growth factor (VEGF) antibodies, and inhibitors of oncogene products.
(3) Epigenetic modulators including peroxisome proliferative activated receptor (PPAR)-agonists (e.g. rosiglitazone and pioglitazone), oestrogen receptor (ER), and histone deacetylase (HDAC) inhibitors.

Agents for colorectal cancer chemoprevention

The most promising chemopreventive drugs are aspirin and the non-steroidal anti-inflammatory drugs (NSAIDs) [4]. Extensive epidemiological observations and laboratory research have suggested that NSAIDs reduce the risk of colon cancer and that the inhibition of colon carcinogenesis by NSAIDs is mediated through the modulation of prostaglandin production by the rate-limiting COX enzymes. NSAIDs reduce the risk of CRC, possibly through a mechanism involving inhibition of COX-2, which is overexpressed in premalignant adenomatous polyps and in CRC. This article will be focused on NSAIDs, mainly selective and natural COX-2 inhibitors.

The preventive efficacy of this class of agents is supported by more than 200 well conducted animal studies. A proof of concept in humans was achieved in familial ademtous polyposis (FAP) patients [5]. Most significantly, in 57 epidemiological studies (out of 62) it was clearly demonstrated that NSAID consumption

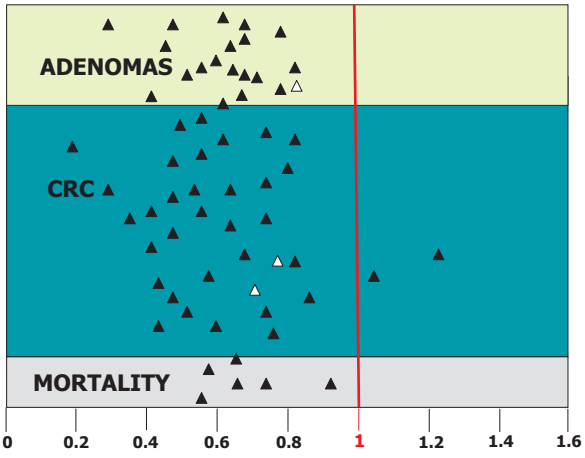

Fig. 1. Relative risk of colorectal neoplasia in individuals using aspirin, NSAIDs and COX-2 inhibitors*. *62 Epidemiological Studies, 1988–2009. White triangles represent recent new studies.

prevents adenoma formation, decreases the incidence of CRC and even reduces the mortality from CRC (Fig. 1) [3]. However, NSAID consumption is not free of toxicity. Previous data in 1997 showed 107,000 hospitalisations and 16,500 deaths in the US alone as a result of NSAID and aspirin consumption [6], equalling the mortality from AIDS or leukaemia.

Gastrointestinal (GI) toxicity constitutes the clinically most relevant complication of NSAID consumption. GI side effects that can contribute to the morbidity and mortality associated with these drugs include upper GI adverse events, such as ulceration, bleeding, perforation, or obstruction, and hepatic injury, that is usually reversible, most likely due to an idiosyncratic reaction resulting from an immunologic response or altered metabolic pathways. GI side effects of NSAIDs are mostly attributed to COX inhibition resulting in reduction of prostaglandin in gastric mucosa. Topical irritant effects are also contributed to their systemic effect of prostaglandin inhibition [7]. Selective COX-2 inhibitors were designed with the claim that they would be devoid of ulcer-promoting effects due to the fact that they would spare gastric mucosal prostaglandin synthesis and would not damage the gastric mucosa [8]. However, this promise has been unfulfilled, and there are concerns about the cardiovascular safety of these inhibitors as discussed herein.

The risks and benefits regarding the use of these agents have been a subject of intensive discussion. Accumulating epidemiologic evidence indicates that aspirin use is associated with reduced risks of CRC. The associations between long-term daily use of aspirin (325 mg/day) and overall cancer incidence were recently examined among 69,810 men and 76,303 women participating in the Cancer Prevention Study II Nutrition Cohort [9]. Aspirin use was reported at enrolment and updated every 2 years. Daily aspirin use, for more than 5 years, was associated with lower incidence of CRC. On the other hand, two large trials of aspirin in primary prevention showed no effect on the occurrence of CRC. The Women's Health Study randomised healthy women to low dose aspirin versus placebo. An average of 10 years of follow-up failed to show a primary preventive effect of aspirin [10]. To date, this is the only randomised controlled trial that has specifically examined the effect of aspirin on the incidence of cancer in healthy people. The Physicians' Health Study was primarily designed to assess the effect of aspirin (325 mg every other day) on the risk of coronary artery disease and cancer in 22,071 male physicians in the US [11]. After 5 years of aspirin therapy, there was no change in the incidence of CRC or adenomatous polyps between the treatment and placebo groups. The randomised trials of short-term duration (up to 4–5 years) have provided compelling evidence of an inverse relationship between aspirin and colorectal neoplasia. Nonetheless, prospective data on long-term risk of CRC according to dose or duration of therapy remain limited. Flossmann and colleagues [12] studied the long-term effect of aspirin in two other trials (the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial) which failed to show a protective effect of aspirin [13,14]. They also performed a systematic review of all relevant observational studies and concluded that the use of >300 mg aspirin per day for at least 5 years in the randomised controlled trials was effective in primary prevention of CRC, with a latency period of about 10 years. However, these studies were unable to circumvent confounders, such as intermittent and variable dosing, use of other NSAIDs and risk-modifying drugs.

An international consensus report was recently published following the 5th International Conference on Cancer Prevention that was held in St Gallen, Switzerland (March 6–8, 2009) [15]. The panel evaluated the use of aspirin and NSAIDs for cancer chemoprevention, and have concluded that the data on the risk-benefit profile for cancer prevention are insufficient and therefore, no definite recommendations can be made. To date, aspirin is the only NSAID with sufficient efficacy and toxicity data that qualifies for a risk-benefit analysis. Therefore, such a panel discussion is critically important. The consensus statement of the panellists stated that additional studies of aspirin and cancer prevention are needed to define the lowest effective dose, the optimal age/s

for treatment initiation and duration, and the target sub-populations which will best benefit from such treatment. In addition, large-scale studies are needed to assess whether long-term aspirin treatment can prevent GI and other cancers.

Chemoprevention of CRC is already possible but drugs that have more acceptable side-effect profiles than the currently available NSAIDs are required. COX-2 specific inhibitors, which should have an improved safety profile, are an ideal drug candidate for the prevention or treatment of CRC, since increased expression of COX-2 is seen through all stages of the multistep process of CRC carcinogenesis and in other solid tumours as well.

Three international, multi-centre, prospective, randomised and placebo-controlled trials in the secondary prevention of CRC were launched in the years 1999 and 2000. The National Cancer Institute (NCI) study, Adenoma Prevention with Celecoxib (APC) trial enrolled 2035 patients from 110 sites in the US, United Kingdom (UK), Canada and Australia. Patients were randomised to receive placebo (679), celecoxib 200 (586) or 400 (671) mg bid. A follow-up colonoscopy was conducted in 89% and 76% of the participants after 1 and 3 years, respectively. In patients taking celecoxib, polyp recurrence was reduced by 33% and 45% for patients taking 400 or 800 mg of the drug ($P < 0.0001$). The relative risk of advanced adenomas (>1 cm, tubulovillous or villous histology, high-grade dysplasia, or invasive cancer) was even more effectively reduced by 57% and 66% in patients taking the two dosages ($P < 0.0001$).

In the second study sponsored by Pfizer, Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP), the effectiveness of celecoxib (400 mg qd) in reducing the incidence of sporadic colorectal adenomas was evaluated. It recruited 1561 patients from 107 sites in 32 countries. Patients were split into a 3:2 ratio of celecoxib (933) and placebo (628) and divided by baseline aspirin use (17%). Of the total patients, 89% and 79% underwent a colonoscopy with or without removal of polyps at 1 year and 3 years, respectively. Celecoxib reduced adenoma recurrence by a third after 1 and 3 years ($P < 0.001$). The incidence of advanced adenoma was reduced by 51%.

In a third study, conducted by Merck, for rofecoxib in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, rofecoxib, 25 mg qd, was evaluated in comparison to placebo. 2547 participants from 110 sites were recruited. A 25% reduction in polyp recurrence was seen after 1 and 3 years.

However, all three studies were terminated earlier than planned due to substantial concern over increased cardiovascular (CVS) toxicity. The CVS toxicity seen in the APPROVe trial caused Merck to withdraw rofecoxib from the market. In the APC trial, the CVS toxicity increased from 1.0% ($n = 7/679$) for placebo to 2.5% ($n = 16/685$) and 3.4% for celecoxib (200 mg bid and 400 mg bid, respectively) ($P < 0.01$). The proportion of all patients experiencing CVS toxicity in the PreSAP trial increased from 1.9% ($n = 12/628$) for placebo to 2.5% ($n = 23/933$) for celecoxib (400 mg qd) ($P = \text{NS}$).

On the other hand, the gastrointestinal toxicity of celecoxib in the PreSAP and APC trials was recently adjudicated. There was no significant difference between the drug and placebo for the entire 3 year duration of the study. Surprisingly, a low dose of aspirin (<100 mg/d) was associated with significantly increased GI complication rate (hazard ratio [HR] 2.93).

This year the results of the studies after 4 (APPROVe) and 5 years (APC and PreSAP) of follow-up are being reported in scientific meetings (data not shown). Interestingly, the drug is still effective (in reducing adenoma recurrence and in particular advanced adenomas) but cardiovascular toxicity still also persists, for up to 2 years after the drug was stopped.

A systematic review examining the benefits and risks of NSAIDs and COX-2 inhibitors for the prevention of CRC and adenomas has recently been prepared for the US Preventive Services Task Force (USPSTF) [16] and concluded that while able to reduce the incidence of colonic adenomas and CRC, these agents are associated with important cardiovascular events and GI toxicity and, therefore, the balance of benefits to risk does not favour chemoprevention in average-risk individuals.

In the intriguing jigsaw puzzle of cancer prevention, we now have a definite positive answer for the basic question of "if", but several other parts of the equation (proper patient selection, ultimate drug, optimal dosage and duration, and best screening modality) are still missing.

Most cancers progress through the action of multiple pathways that include COX-2, Wnt-β-catenin, mitogen-activated protein kinase (MAPK), cytokines and growth factor signalling. Drugs that simultaneously block several pathways might be particularly effective as chemopreventive agents [15].

Receptor tyrosine kinases (RTKs) regulate cellular proliferation and differentiation and are overexpressed in many invasive cancers, including CRC. Therefore, RTKs and their ligands are appealing molecular

targets, either for direct modulation or indirect control of their downstream effects and signalling pathways.

EKB-569, an irreversible inhibitor of EGFR, was shown to be highly protective against intestinal neoplasia in *ApcMin/+* mice. Thus, untreated *ApcMin/+* mice developed polyps, whereas nearly half of the mice treated with EKB-569 in combination with sulindac developed no polyps [17]. Similarly, another study has shown that inhibition of insulin growth factor-1 receptor tyrosine kinase (IGF-1R-TK) is a promising novel approach for either mono- or combination treatment strategies of CRC [18]. Anti-EGFR monoclonal antibodies and other small molecule receptor inhibitors, alone or in combination with other agents, are currently under evaluation for CRC chemoprevention.

PPARγ is a nuclear hormone receptor that provides a direct link between fatty acid metabolism and control of gene transcription. Activation of the PPARγ pathway in CRC cells has potent anti-proliferative effects, suggesting that this nuclear hormone receptor may provide a novel target for prevention and treatment of CRC in humans [19].

The ER has been suggested as a potential target for CRC chemoprevention based on observational studies and randomised clinical trials that have looked at the effect of hormone replacement therapy (HRT) on the risk of CRC. In the Women's Health Initiative (WHI) trial, 16,608 postmenopausal women aged 50–79 years, were randomly assigned to a combination of conjugated equine oestrogens (0.625 mg/day) plus medroxyprogesterone (2.5 mg/day) or placebo. The study included 43 invasive CRCs in the hormone group and 72 in the placebo group (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.38–0.81; $P = 0.003$). The invasive CRCs in the hormone group were similar in histological features and grade to those in the placebo group but with a greater number of positive lymph nodes and more advanced stage. The study concluded that relatively short-term use of oestrogen plus progestin was associated with a decreased risk of CRC [20]. Another study has examined the relation of postmenopausal hormone therapy to colorectal adenoma and cancer in a prospective cohort and nested case-control study. The Nurses' Health Study included 59,002 postmenopausal participants and showed that current use of postmenopausal hormones was associated with a decreased risk for CRC (relative risk [RR] 0.65, 95%CI 0.50–0.83). This association was attenuated in past users (RR 0.84, 95%CI 0.67–1.05) and disappeared 5 years after hormone use was discontinued (RR 0.92, 95% 0.70–1.21) [21].

Epigenetic changes can be reversed by the use of small molecules and, thus, such changes are promising targets for cancer chemopreventive drug development [22]. The ability of HDACs to modify the epigenome is under investigation. These drugs induce cell cycle arrest, apoptosis, and/or differentiation in transformed cells *in vitro* and suppress the growth of a wide variety of solid tumour xenografts with relatively minimal toxicity.

Patient's selection

In most studies the preventive agent was particularly effective in preventing high-risk advanced adenomas, as well as adenomas in high-risk subjects. In some subjects, polyp recurrence occurred despite optimal colonoscopic surveillance (up to four during a 5-year period), emphasising the point that only colonoscopies might not be sufficient in high-risk subjects and high-risk adenomas, and a chemopreventive agent can have an added value. In addition, these trials found that patients who developed adenomas despite the ingestion of a chemopreventive agent had fewer and smaller adenomas than the ones in patients who received a placebo. This finding is significant because small tubular adenomas are unlikely to progress to malignancy.

Duration of therapy

Polyp recurrence rate has been shown to be reduced, to the same extent, after 1 and 3 years of therapy in most of the chemopreventive studies. These data suggest that 1 year of therapy might be sufficient to prevent polyp recurrence. Given that it is quite possible that shorter treatment duration would reduce treatment toxicity, chemopreventive agents should theoretically retain their anti-tumour efficacy while reducing their profile of side effects, and in particular cardiovascular and gastrointestinal toxicities.

To ignore the potential benefit of chemoprevention is to continue to accept a higher than necessary death rate from CRC in patient populations who are not fully compliant with screening for CRC.

We are just beginning to understand early tumour formation in a way that permits development of mechanism-based chemoprevention therapies. Moving the field of CRC prevention forward will require a better understanding of the molecular alterations associated with early tumour formation that could be targets for pharmacological intervention, as well as identification of individual factors involved in cancer

risk and treatment toxicity so that interventions can be optimised [23].

There are a number of potentially important modifiers to consider when evaluating the comparative efficacy and toxicity of the chemopreventive agents, and in particular the use of other drugs and polymorphisms in key proteins (metabolising enzymes) that are associated with the degradation of the drugs.

Personalised prevention

When possible, medical treatment should be personalised, i.e. prescription of a specific therapy based on the metabolic characteristics of an individual and the molecular profile of the target lesion. For example, the mechanisms by which NSAIDs and aspirin prevent CRC carcinogenesis are not fully understood. If the agents principally work via COX-2 inhibition, then their use should preferentially reduce the risk of tumours that overexpress COX-2. Indeed, the effect of aspirin differs significantly according to COX-2 expression [24]. Chan and colleagues [25] recently reported that regular aspirin use reduced the risk of CRC in COX-2-expressing cancers, but not in cancers with weak or absent COX-2 expression. The protective effect on COX-2 overexpressing cancers was significantly stronger with an increase in both aspirin dose and duration of use. No such association was observed for cancers with weak or absent COX-2 expression.

Polymorphisms in NSAID targets or metabolising enzymes may affect NSAID efficacy and/or toxicity [26]. The current literature on gene–drug interactions between NSAID use and polymorphisms (e.g. on COX-1 P17L or COX-2 –765G>C) is still very limited and most studies were of limited sample size. Reliable detection of gene–NSAID interactions will require greater sample sizes, consistent definitions of NSAID use, and evaluation of clinical trial subjects in chemoprevention studies [27].

Combination therapy

Although many single agents have potential benefits, their chemopreventive efficacy in clinical trials has been modest, and/or they have an unacceptable toxicity profile [24]. Combining low doses of different agents may be effective in increasing the efficacy while minimising toxicity. In animal models of carcinogen-induced aberrant crypt foci (ACF), a greater reduction in the number of ACF was reported in rats receiving both statin and sulindac compared to each of the drugs alone [28,29]. Another study revealed that combined treatment comprised of piroxicam plus difluoromethylornithine (DFMO) was much more effective than either agent alone [30]. The combination of the turmeric extract, curcumin, with low doses of celecoxib (2–5 μM) was also highly potent. This synergistic effect is clinically important since it can be achieved in human serum following standard anti-inflammatory or anti-neoplastic dosages of celecoxib (200–400 mg per day) [31].

Following these impressive results in the preclinical setting, combinatorial treatment is currently under extensive study. A large randomised study on the effect of celecoxib with or without DFMO in patients with FAP is underway at the MD Anderson Cancer Center in conjunction with the NCI (Dr. P. Lynch, MD Anderson Cancer Center). Results are expected in 2009. DFMO is being studied in combination with sulindac in another phase III study in patients with a history of sporadic adenomas [32]. In this placebo-controlled study a low dose combination of DFMO (500 mg) and sulindac (150 mg) was administered once daily in patients with history of sporadic adenomas. The study was planned for 3 years; however, after the first interim analysis, the Data Safety Monitoring Board (DSMB) recommended that the study be terminated early because it had already met its endpoint. In the active treatment arm, 12.3% had developed at least one adenoma compared with 41.1% in the placebo arm, which represents a 70% risk reduction. The difference was even more pronounced for advanced adenomas (RR reduction of 92%) although only a small number of advanced lesions (11 versus 1; 8.5% versus 0.7%) were detected in this study. There was no significant difference in serious side effects.

Conclusions

Given the large patient numbers, and long periods of follow-up necessary to detect the endpoint, i.e. adenoma or cancer, chemoprevention trials are an enormous expense and a major challenge.

The COX-2 story has demonstrated that administrating an agent over a long period of time is unpredictable and can lead to discontinuation of drugs that millions of dollars have been invested into for their development. Preclinical study and basic research is required to guide a better selection of drugs for further study and to determine ideal intermediate surrogate markers.

In the meantime, for CRC, the only approved chemopreventive agent is celecoxib and only for high-risk patients with FAP. Sulindac has also repeatedly

demonstrated efficacy in this setting. However, due to the high incidence of GI toxicity associated with sulindac, its benefit will have to be weighed against the risk. FAP patients are usually young subjects with minimal cardiovascular risks, and a 100% likelihood of CRC development. Hence, they do represent an ideal group to consume COX-2 inhibitors.

In addition to benefit versus harm in treatment with these agents, any health policy aimed at chemoprevention needs to take into consideration the cost of the drug and cost of side effects associated with long-term treatment. Studies comparing chronic use of NSAIDs, including aspirin [33,34], and COX-2 inhibitors [35] with colonoscopy every 10 years for prevention of CRC cancer found that their use in preventing CRC saves fewer lives at higher costs, even before the risks of COX-2 inhibitors were realised. This renders screening colonoscopy a more cost-effective strategy to prevent CRC. It is important to find the correct place for chemopreventive agents in the enormous challenge of cancer prevention. It is possible that chemoprevention might lengthen the periods required between colonoscopies or replace surveillance colonoscopies in patients that refuse/or are unable to have them done. Chemoprevention might be optimally used only in high-risk patients with advanced adenomas. In this setting polyp recurrence approaches 50% even with shortened intervals of colonoscopic surveillance (1–3 years) [36,37]. Proof of concept has been achieved and the future should focus on finding the ideal drug and ways to stratify subjects in order to determine who will benefit the most and be harmed the least.

Conflict of interest statement

None declared.

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