Cyclooxygenase-2 Inhibitors in Colorectal Cancer Prevention: Point

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Abstract

The limited success of current treatments for most advanced common malignancies highlights the importance of cancer prevention. Clinical trials on cyclooxygenase (COX) inhibitor drugs showed the potential of chemoprevention as a strategy for reducing cancer incidence, although not without associated side effects. The attractiveness of these drugs partly stems from an ability to engage multiple mechanisms of action by their potential to influence multiple components of the carcinogenesis pathway, from initiation to progression. There are two isoforms of the COX enzymes. COX-1 is constitutively expressed in normal tissues and serves as a "housekeeper" of mucosal integrity, whereas COX-2 is an immediate early response gene that is highly inducible by neoplastic and inflammatory stimuli. COX-2 is significantly overexpressed in colorectal neoplasms, making it an attractive therapeutic target. The drug market has been revolutionized by the development of preparations targeted selectively against COX-2, and a proof of concept has been achieved. Chemoprevention of colorectal cancer is already possible with celecoxib, but it is still not the ultimate drug of choice especially because of the cardiovascular risk associated with COX-2 inhibitors. Better patient selection and more effective and safer drugs are needed. Celecoxib is probably best used in a subset of individuals at moderate to high colorectal cancer risk and low risk of cardiovascular disease.

Introduction

Colorectal cancer is a major health concern, with more than 1 million new cases and 500,000 deaths expected worldwide in 2007 (1). Chemoprevention is an emerging science that offers a promising approach for reducing mortality from colorectal cancer. Colorectal cancer meets the criteria of a disease suitable for chemopreventive interventions by being one that is prevalent as well as associated with considerable mortality and morbidity rates. Moreover, it has a natural history of transition from precursor to malignant lesion that spans, on an average, over 15 to 20 years, providing a window of opportunities for effective interventions and prevention.

Chemoprevention involves the long-term use of oral agents that can delay, prevent, or even reverse the development of cancer, by interfering with its multistep progression. Chemoprevention interferes in this process of carcinogenesis by targeting key molecular pathways. Chemoprevention may be of particular importance to individuals with a hereditary predisposition to colorectal neoplasia. The scientific basis of chemoprevention has evolved over the last two decades and represents a potential approach to reducing the incidence of and mortality from cancer.

COX and Cancer

Cyclooxygenase (COX) or prostaglandin-endoperoxide synthase is probably the most common therapeutic drug target in human history. It oxidizes arachidonic acid to prostaglandin G2, reduces prostaglandin G2 to prostaglandin H2, and is the key enzyme responsible for the production of prostaglandins and other eicosanoids. Inhibitors of this enzyme have been used for thousands of years by more than 1 billion people worldwide.

The hypothesis that nonsteroidal anti-inflammatory drugs (NSAID) might inhibit the occurrence or growth of colorectal cancer was put forth in the mid-1970s. Bennett and Del Tacca (2) and Jaffe (3) reported that the concentration of prostaglandin E2 was significantly higher in colorectal cancer tissue than in the surrounding normal mucosa. The mechanism for cancer protection is unknown, but it may relate to altered synthesis of arachidonic acid metabolites. These compounds modulate a number of signal transduction pathways that may affect proliferation, programmed cell death (apoptosis), angiogenesis, immune response, cellular adhesion, differentiation, and tumor invasion.

The past three decades have witnessed more than 200 well-conducted, randomized, single blind, placebo-controlled animal studies that showed the consistent preventive effect of aspirin and NSAIDs on carcinogen-induced colorectal neoplasia in rodents. Those experiments showed that the administration of aspirin and a variety of NSAIDs in combination with a colon carcinogen results in fewer colorectal tumors per animal and fewer animals with tumors compared with control groups (for review, see refs. 4, 5).

Kune et al. (6) reported the first population-based case-control study that showed a relative risk of 0.53% for...
colorectal cancer among regular aspirin consumers compared with nonusers. In 56 of the subsequent 58 epidemiologic studies comprising tens of thousands of subjects, the protective effect of regular use of aspirin, NSAIDs, or COX-2 inhibitors was clearly shown by lowering the risk for colorectal cancer by ~50% (Fig. 1). These studies were undertaken in a variety of settings (retrospective, prospective, cohort, and case-control studies). The protective effect in terms of preventing adenoma recurrence, decreasing colorectal cancer incidence, and even reducing the colorectal cancer mortality rate was seen in both women and men and in all age groups. It was shown to depend on the dose and type of the drug, but more importantly, on the duration of exposure (for reviews, see refs. 4, 5, 7).

The use of aspirin and nonspecific NSAIDs is, however, associated with gastrointestinal and renal toxicity caused by the inhibition of COX-1. In 2002, 260,000 hospitalizations and 26,000 deaths were due to NSAID and aspirin consumption in the United States alone (8).

One of the primary pharmacologic properties of NSAIDs is their ability to inhibit the COX enzymes. The differences between the two COX isoforms lie in their distribution in the body and in their physiologic function. COX-1 is expressed constitutively in many tissues, and it plays a central role in platelet aggregation and gastric cytoprotection (9). COX-2 is not expressed in normal-appearing mucosa. It is induced in many tissues during inflammation, wound healing, and neoplasia. COX-2 is the important isoform in the pathogenesis of colorectal cancer. Increased expression of COX-2 probably occurs during all stages of the multistep progression of colorectal cancer, from the first genetically altered cell, through hyperplasia, dysplasia, carcinoma, and even metastasis (10-12). The association between COX-2 and colorectal cancer led many scientists and clinicians to investigate whether the inhibition of this pathway could provide some reduction in colorectal cancer risk.

In the early 1990s, the pharmaceutical industry began to develop specific COX-2 inhibitors that do not affect COX-1 activity. These COX-2 inhibitors were refined and approved for use for the indications of pain, fever, inflammation, and arthritis.

Direct genetic evidence of the role of COX-2 in colorectal cancer was provided by Oshima et al. (13) in a landmark study using APC716 knockout mice. These mice harbor a truncation mutation in the APC gene and develop hundreds of polyps in their intestinal tracts. Compared with control APC716 knockout mice, the number of intestinal polyps was reduced by 34% when one of the COX-2 alleles was knocked out. When both COX-2 alleles were deleted, there was an 86% reduction in polyp count and this reduction was accompanied by a reduction in average polyp size.

Dubois et al. (10) were the first to report increased expression of COX-2 in colorectal cancer, without changes in COX-1 levels. Their original observation was followed by several reports that confirmed increased COX-2 expression in this setting (4, 5).

COX-2 is an important player in colorectal cancer carcinogenesis, yet it is also possible that COX-2 inhibitors act by COX-2–independent mechanisms. Cells that do not express COX-2 also undergo apoptosis in response to exposure to NSAIDs. Inhibition of the activity of nuclear factor-κB, interference with the binding of the peroxisome proliferator activating receptor-δ to DNA, activation of peroxisome proliferator activating receptor-γ, activation of protein kinase G, and down-regulation of the antiapoptotic protein Bcl-XL were all suggested as putative non–COX-2 targets of COX-2.

**Figure 1.** Relative risk of colorectal neoplasia in individuals using aspirin, NSAIDs, or COX-2 inhibitors. CRC, colorectal cancer.
inhibitors (4, 5, 7, 8). The presence of multiple molecular targets offers the potential for combination therapies, which may be more effective than any agent alone.

The first clinical trial in cancer prevention using the COX-2 inhibitor was carried out in the setting of familial adenomatous polyposis patients with intact colon (14). It was a randomized, double blind, placebo-controlled trial of celecoxib (Celebrex, Pfizer). Eighty-one patients from London (St. Mark’s Hospital) and Houston (M. D. Anderson Medical Center) were randomly selected to receive two dosages of the drug (400 or 800 mg) or a placebo, every day for 6 months. Upon completion of the study, a significant reduction in polyp burden (by ~30%) was observed in patients who received the higher dose. A different approach was taken in another prospective small study (15). Rofecoxib (25 mg every day) was given for 30 months and sigmoidoscopy/colonoscopy was done at study entry and every 6 months thereafter. The number, size, and histologic grade of all polyps were assessed, and the polyps were removed during each endoscopic procedure. In that open-label study, the efficacy of the combined approach of endoscopy and chemoprevention was shown with a highly significant reduction in the rate of polyp formation (by 70-100%) at the end of the study (15).

Three international multicenter studies were launched in 1999 and 2000 to evaluate the efficacy and safety of the new COX-2–specific inhibitors in preventing the recurrence of sporadic colorectal polyps. The design of these trials was similar and required continuous treatment for 3 years, with a 2-year extension to evaluate drug safety. Each study recruited between 1,500 and 2,600 subjects who had undergone a recent adenoma removal and who came from over 100 geographic locations. The primary end point was the number of patients with polyps. The Adenomatous Polypl Prevention on Vioxx trial recruited a total of 2,586 patients. They were assigned to receive rofecoxib (Vioxx, Merck Sharp and Dohme) 25 mg daily (1,257 patients) or placebo (1,299 patients). A 25% reduction in adenoma recurrence was found in the treatment group (16). The Adenoma Prevention with Celecoxib (APC) trial included 2,026 patients with a recently removed adenomatous polyp. They were at high risk of recurrent adenomas (e.g., based on a history of either multiple adenomas or removal of a single adenoma more than 5 mm in diameter), and were randomized to either placebo or celecoxib (200 or 400 mg twice daily). These patients were followed up for a mean of 33 months while taking the study drug. The results at the 3-year follow-up revealed a significant reduction in polyp recurrence (P < 0.0001; ref. 17). The Prevention of Sporadic Adenomatous Polyps (PreSAP) trial was conducted in parallel to the APC trial for the same indication: 1,561 patients from 106 medical centers in 32 countries from 6 continents were randomized (3:2) to receive either celecoxib (400 mg qd) or placebo (18). The adenoma recurrence rate was 33% in the celecoxib group versus 49.3% in the placebo group (P < 0.0001). Note-worthy was that all these studies showed a greater effect on advanced adenomas (16-18).

The results of these cancer prevention trials generated an enormous amount of worldwide attention, mainly due to unexpected cardiovascular side effects. These side effects would have not been detected in a 12-month study because there was no significant difference between the placebo and treated groups during that time frame. On September 25, 2004, Merck dramatically announced the early termination of their study. This decision was made even before the efficacy of the drug had been evaluated. Vioxx was withdrawn from the market due to increased cardiovascular toxicity in patients who had been receiving the drug for more than 18 months. A total of 46 patients in the rofecoxib group had a confirmed thrombotic event compared with 26 patients in the placebo group (relative risk: 1.92; ref. 19). On December 9, 2004, the Food and Drug Administration issued a “black box” warning for valdecoxib (Bextra, Pfizer) due to increased cardiovascular risk in patients undergoing coronary artery bypass (20). On December 17, 2004, the National Cancer Institute suspended the APC trial because the analysis by an independent cardiovascular adjudication committee, a subcommittee of its Data Safety and Monitoring Board, discovered a significant dose-response excess of major cardiovascular events of 2.5 and 3.5 for the celecoxib 200 and 400 mg bid groups, respectively, compared with the placebo group (21). The absolute excess of major cardiovascular events in this trial is similar in magnitude to the results of the trials with rofecoxib and valdecoxib. At the same time, the Data Safety and Monitoring Board of the PreSAP trial also suggested the cessation of drug distribution, although no excessive cardiovascular toxicity was observed in that trial. The relative risk of the celecoxib 400 mg qd group compared with the placebo group was nonsignificant at 1.3 (18).

There are two plausible explanations for the discrepancy between the two celecoxib trials. Most obvious is the dosing difference. In the APC trial, the drug was given twice daily for a total daily dose of 400 or 800 mg, with the likelihood of side effects being greater with increasing dose. It is also possible the once daily PreSAP dose of 400 mg is less toxic than 200 mg bid due to the relatively short half-life of celecoxib. It has been hypothesized that the suppression of COX-2–dependent prostacyclin formation could augment the response to thrombotic and hypertensive stimuli and initiate accelerated atherogenesis (22, 23).

Many questions remain unanswered about the actual mechanisms and the magnitude of the cardiovascular risk associated with the use of COX-2–selective inhibitors. The adenoma prevention trials were not designed to study cardiovascular events; they included very low numbers of events and it was difficult to control for confounding variables. Moreover, there is ample evidence suggesting increased cardiovascular toxicity that is associated with the use of nonselective NSAIDs (24).

Bertagnolli analyzed the data from the APC and the PreSAP trials and showed that 27 and 15 fewer patients per 1,000 per year, respectively, developed advanced colorectal adenomas, at a cost of ~5 and 2 additional patients per 1,000 per year, respectively, who experienced a serious cardiovascular adverse event. These data show that, with a few exceptions, most patients tolerated 3 years of continuous celecoxib use without drug-related toxicity (25).

In both the APC and the PreSAP trials, celecoxib was particularly effective in preventing high-risk advanced adenomas, which were relatively common in the placebo group (17.2% and 10.4%, respectively) despite optimal colonoscopic surveillance (three colonoscopies...
in 3 years). In addition, both of these trials found that patients who developed adenomas despite the ingestion of celecoxib had fewer and smaller tumors than the ones in patients who received a placebo. This finding is important because small tubular adenomas are unlikely to progress to malignancy. It is encouraging that celecoxib did not simply reduce tumor number; it also eliminated the more serious lesions and reduced the overall burden of disease in susceptible individuals (16-18).

An additional contribution of the design of the COX-2 inhibitor studies was the inclusion of a surveillance colonoscopy after only 1 year of study drug use. The polyp recurrence rate was reduced to the same extent after 1 and 3 years in all the different subgroups in all three COX-2 inhibitor 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, celecoxib should theoretically retain its antitumor efficacy while reducing cardiovascular toxicity by following a shorter duration dosing schedule.

A comparison of results from the APC and the PreSAP studies suggests that once-daily dosing at 400 mg is safer than a twice daily dose of 200 mg while still retaining significant antitumor efficacy. Unfortunately, because neither of these trials was designed or powered to assess cardiovascular toxicity, no firm conclusion can be reached without further study in a randomized trial. Knowledge of the duration of protection is important and it will be available in 2008 when the analysis of the 2-year extension (on study/off drug) of the PreSAP and the APC studies is completed.

The unexpected identification of cardiovascular toxicity related to selective COX-2 inhibitors has understandably made it more difficult for new agent development in this field. To ignore the potential benefit of chemoprevention, however, is to continue to accept a higher than necessary death rate from colorectal cancer in patient populations who are not fully compliant with screening for colorectal neoplasia. We are just beginning to understand early tumor formation in a way that permits the development of mechanism-based chemoprevention therapies. Moving the field of colorectal cancer prevention forward will require a better understanding of the molecular alterations associated with early tumor formation that could be targets for pharmacologic intervention, as well as identification of individual factors involved in cancer risk and treatment toxicity so that interventions can be optimized (26).

There are a number of potentially important modifiers to consider when evaluating the comparative gastrointestinal toxicity of NSAIDs and COX-2 inhibitors. Two stand out: co-ingestion of low-dose aspirin for cardiovascular prophylaxis and infection with *Helicobacter pylori*. The strongest evidence for aspirin comes from large, randomized trials. The majority of the ones that examined this interaction found that any advantage of COX-2 inhibitors is probably lost in patients who co-ingest low-dose aspirin for the prevention of cardiovascular events (22, 23, 27). When aspirin is given with a proton-pump inhibitor, however, especially after *H. pylori* eradication, the risk of bleeding complications following aspirin or NSAID use is dramatically decreased (by 50-90%; refs. 28, 29).

### Personalized Prevention

Chemopreventive actions may not benefit all individuals (30). A potential explanation for this diversity may be the presence of variably increased metabolizing enzymes, especially prostaglandin H synthase 2 and the uridine diphosphatidyl glucotransferase polymorphisms, which increase chemopreventive efficacy by up to 50% (31, 32).

When possible, medical treatment should be personalized; that is, 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 colorectal cancer carcinogenesis are not fully understood. If the agents principally work via COX-2 inhibition, then their use should preferentially reduce the risk of tumors that overexpress COX-2. Indeed, the effect of aspirin differs significantly according to COX-2 expression. Chan et al. (33) recently reported that regular aspirin use reduced the risk of colorectal cancer 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 increasing 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 metabolizing enzymes may affect NSAID efficacy and/or toxicity (34). The current literature on these interactions is still very limited (e.g., on COX1 P17L or COX2 -765C>G). 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 (35).

### Combination Therapy

Although many single agents have potential benefits, their chemopreventive efficacy in clinical trials has been modest (15-20%), and/or they have an unacceptable toxicity profile. Combining low doses of different agents may be effective in increasing the efficacy while minimizing toxicity. In animal models of carcinogen-induced aberrant crypt foci, a greater reduction in the number of aberrant crypt foci was reported in rats receiving both a statin and sulindac compared with each of the drugs alone (36, 37). Another study revealed that combined treatment composed of piroxicam plus difluoromethylornithine was much more effective than either agent alone (38). The combination of the turmeric extract, curcumin, with low doses of celecoxib (2.5 μmol/L) potentiates the growth inhibitory effect of either drug alone. This synergistic effect is clinically important because it can be achieved in human serum following standard anti-inflammatory or antineoplastic dosages of celecoxib (200-400 mg/d; ref. 24).

Following these impressive results in the preclinical setting, combination treatment is currently under extensive study in the chemopreventive field. A large randomized study on the effect of celecoxib with or without piroxicam plus difluoromethylornithine in patients with familial adenomatous polyposis is underway at the M. D. Anderson Cancer Center in conjunction...
Discussion

Where do we stand on the use of COX-2 inhibitors in the prevention of colorectal neoplasia? The use of these agents is clearly associated with a significant reduction in the risk of adenoma recurrence, particularly advanced adenomas that possess the highest risk for malignant transformation (16-18). At the same time, it seems unlikely that even a small increase in cardiovascular risk will be tolerated in otherwise healthy individuals. The risk of colorectal cancer occurrence in these individuals is low, provided that they are enrolled in a colonoscopy surveillance program. On the other hand, the benefits of COX-2 inhibitors may suggest their use in subjects with low cardiovascular risk who are at moderate to high risk, such as colorectal cancer survivors, subjects with recurrent high-risk adenomas, or those with familial cancer syndromes. In fact, celecoxib is approved by the Food and Drug Administration as an adjunct therapy in familial adenomatous polyposis patients. It may be appropriate to consider the use of celecoxib (400 mg qd) as a chemopreventive agent in healthy individuals who have a low cardiovascular risk and a moderate-to-high risk for colorectal cancer, such as the case illustrated below.

A 40-year-old, thin, healthy woman with a strong family history of colorectal cancer (but without an inherited syndrome) and no cardiovascular risk factors underwent screening colonoscopy. She had a tortuous colon with some adhesions (history of two cesarean sections). Two large sessile polyps were identified in the right colon. Polypectomy was successful, but the massive bleeding that resulted was difficult to control by endoscopic means. She received 4 units of blood and was discharged from hospital after 72 hours. Histology revealed villous adenoma with a few foci of high-grade dysplasia. The polyps had been completely excised. The patient understands the need for frequent surveillance colonoscopies, but she is also interested in any other therapeutic options that can prevent or decrease the likelihood of polyp recurrence. For a case such as this, it seems reasonable to prescribe once daily celecoxib 400 mg for 1 year, keeping in mind that the rate of polyp recurrence after 1 and 3 years was identical in all three COX-2 inhibitor trials (16-18), or even higher at 1 year (16). Celecoxib will not eliminate the need for another colonoscopy but it may substantially decrease the chance of recurrence of advanced adenomas.

The recent history of COX-2 has shown that long-term ingestion of an agent that is apparently safe when used for a short time may be unpredictable in its actions and can lead to serious adverse effects. Preclinical study and pharmacogenomic research are required to establish guidelines for a better selection of drugs for further study and to determine ideal intermediate surrogate markers.

Realistically, all drugs will have some side effects that need to be taken into consideration. It should be emphasized that only very few drugs have been examined over such a long period and with sufficient study participants as COX-2 inhibitors (16-18). There may be drugs, currently on the market, which would not stand up to the scrutiny in terms of safety and efficacy. Although toxic side effects of medications may be acceptable and almost inevitable in the treatment of advanced cancers as they are with chemotherapy, they are not tolerated in chemoprevention (27).

The safety profile of COX-2 inhibitors varies from drug to drug. Concerns regarding rofecoxib were grave enough to remove the drug from the market. Celecoxib at a once daily dose of 400 mg seems to be fairly well tolerated and effective, in particular in the prevention of advanced adenomas.

It is unlikely that chemoprevention will completely replace screening, but its success may lead to the need for fewer screening exams and to fewer cancer-related deaths from interval cancers, especially in high-risk groups.

Recommendations

When considering the use of COX-2 inhibitors, it is suggested that (a) their use be confined to high-risk patients, or selected moderate-risk patients; (b) any existing H. pylori infection should be eradicated; (c) patients with cardiovascular risk factors should be excluded; and (d) it is possible that the benefit of cardiovascular prophylaxis versus the risk of gastrointestinal side effects might favor using low-dose aspirin with celecoxib.

The ideal chemopreventive agent remains elusive given the emphasis on the caveat not to harm. Combinations of agents may hold the answers to maximizing effectiveness while limiting drug toxicity. Finally, individualized approaches would provide the ability to predict both risk and benefit for any given subject based on specific single-nucleotide polymorphisms or other genetic profiles (39).

A proof of concept has been achieved. Now, more trials are needed with better patient characterization and superior drug selection.

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No potential conflicts of interest were disclosed.

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1 PI Patrick Lynch, personal communication.
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