COX-2 Active Agents in the Chemoprevention of Colorectal Cancer

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Abstract

Chemopreventive strategies for colorectal cancer (CRC) have been extensively studied to prevent the recurrence of adenomas and/or delay their development in the gastrointestinal tract. The non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors have been proven as promising and the most attractive candidates for CRC clinical chemoprevention. The preventive efficacy of these agents is supported by a large number of animal and epidemiological studies which have clearly demonstrated that NSAID consumption prevents adenoma formation and decreases the incidence of, and mortality from CRC. On the basis of these studies, aspirin chemoprevention may be effective in preventing CRC within the general population, while aspirin and celecoxib may be effective in preventing adenomas in patients after polypectomy. Nevertheless, the consumption of NSAID and COX-2 inhibitors is not toxic free. Well-known serious adverse events to the gastrointestinal, renal and cardiovascular systems have been reported. These reports have led to some promising studies related to the use of lower doses and in combination with other chemopreventive agents and shown efficacy. In the intriguing jigsaw puzzle of cancer prevention, we now have a definite positive answer for the basic question

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"if", but several other parts of the equation-proper patient selection, the ultimate drug, optimal dosage and duration are still missing.

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Colorectal cancer (CRC) is a major health concern worldwide. In 2011 alone, 1,200,000 new cases of CRC and more than 600,000 deaths from the disease are predicted. Sporadic CRC has a natural history of evolution from normal mucosa to adenoma to overt cancer that spans on average 10–20 years, thereby providing a window of opportunity for effective intervention and prevention. CRC can be prevented by lifestyle modification (i.e. regular physical activity, smoking abstinence, and healthy nutrition) and screening and surveillance strategies. However, although these strategies are standard clinical practice, their impact is limited due to low adherence. The number of deaths due to this disease remains alarmingly high, and makes CRC prevention paramount.

Chemoprevention interferes with the process of carcinogenesis by targeting key molecular pathways that provides a promising approach to reduce the incidence of and mortality from cancer. Chemoprevention of CRC involves the use of a variety of natural or chemical compounds that can delay, prevent, or even reverse the adenoma to carcinoma process in the colon. CRC fits the criteria for chemopreventive intervention as adenomatous polyps are identifiable and treatable therefore, allowing implementation of therapeutic and preventative strategies (Arber 2008).

Based on reports of chemopreventive activity in the literature and/or efficacy data from in vitro models of carcinogenesis, several agents have been studied including, phytochemicals, vitamins, minerals, inhibitors of proliferation, metabolic inducers, non-steroidal anti-inflammatory drugs (NSAIDs), and differentiation agents. Representative examples include, folic acid, calcium, estrogen, vitamin D, olpitraz, curcumin, selenium, green tea, ursodiol, statins, and fiber, which have been encouraging, but shown modest efficacy in humans.

The most promising drugs are aspirin and NSAIDs, and much of their effect has been attributed to their potent inhibition of the cyclooxygenase (COX) enzymes (Fig. 1).

The COX enzyme is probably the most common therapeutic drug target in human history. Aspirin, a COX Inhibitor, has been used for almost 4000 years, and large amounts of these compounds are consumed each year. Research in this area has been dominated by investigations into the COX enzymes, also known as prostaglandin-endoperoxide synthases, which are central and rate-limiting enzymes in the biosynthesis of prostaglandins (Arber 2008; Tuynman 2004). Three COX isoforms have been identified: COX-1, COX-2, and COX-3.

COX-1 and COX-2 are located on different chromosomes and their expression is tightly regulated (Tuynman 2004). COX-1 is mapped to chromosome 9q32-q33.2, is encoded by the *PTGS1* gene, and constitutively expressed in normal

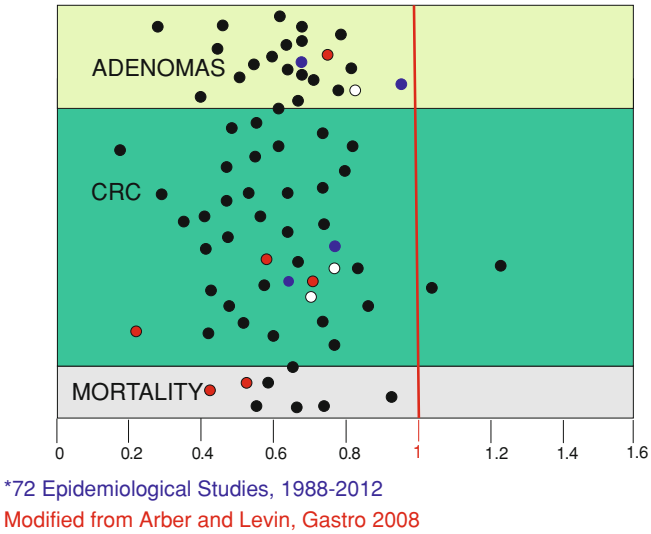

Fig. 1 Relative risk of colorectal neoplasia in individuals using aspirin, NSAIDs and COX-2 inhibitors

tissues. It serves as a 'housekeeper' of mucosal integrity. COX-1 is the central enzyme in the biosynthetic pathway to prostaglandins from arachidonic acid, it produces prostacyclins, prostaglandins, and thromboxane, which protect gastric mucosa and play a key role in platelet aggregation and renal microvasculature dynamics. COX-2 is mapped to chromosome 1q25.2-q25.3, and is encoded by the *PTGS2* gene, an immediate early response gene that is highly inducible by either neoplastic or inflammatory stimuli. COX-2 is involved in the synthesis of prostaglandins and thromboxanes, which are regulators of processes that are relevant to cancer development. It is generally accepted that alterations in COX-2 expression and the abundance of its enzymatic product prostaglandin E_2 (PGE_2) have key roles in influencing the development of CRC.

COX-3, a third distinct COX isozyme is a COX-1 variant formed by intron retention, a form of alternative splicing (Chandrasekharan 2002). COX-3 shares all the catalytic features of COX-1 and -2; however, its exact role is yet to be fully understood (Chandrasekharan 2002).

Relative to normal mucosa, COX-2 overexpression occurs in about half of CR adenomas and in 85% of human CRCs, making COX-2 an attractive therapeutic target (Elder et al. 2002; Sheehan et al. 1999). Moreover, the fact that COX-2 expression is up-regulated in both pre-malignant and malignant CR tissue has also potential implications for the prevention of this type of cancer. Already 40 years ago, NSAIDs were hypothesized to inhibit the growth of CRC after a significant decrease in PGE_2 was observed in CRC tissue compared to the normal surrounding mucosa (Bennett and Del Tacca 1975; Jaffe 1974). The preventive efficacy of this class of agents is supported by more than 300 animal studies. Most significantly,

70 out of 72 epidemiological studies clearly demonstrated that NSAID/aspirin consumption prevents adenoma formation and decreases the incidence of, and mortality from, CRC (Fig. 1). However, NSAID consumption is not free of toxicities. There are well-known serious adverse events to the gastrointestinal, renal, and cardiovascular systems. In the United States alone, 260,000 hospitalizations and 26,000 deaths were attributed to NSAID consumption in 2002 (Grover et al. 2003).

Since COX-2-selective inhibitors do not inhibit COX-1, they are not generally believed to harm the normal mucosa. However, because COX-2 is overexpressed throughout the multistep process of CRC carcinogenesis, they would seem to be an ideal drug candidate for use in the healthy population for the prevention of CRC. In the early 1990's, pharmaceutical companies began developing COX-2 selective inhibitors with minimal effect on COX-1 activity (Arber 2008). In 1999 and 2000 three international, multicenter, prospective, randomized, placebo-controlled trials in the secondary prevention of CRC were launched (Baron et al. 2006; Bertagnolli et al. 2006, 2009; Bresalier et al. 2005). These clinical trials demonstrated the efficacy of COX-2 inhibitors as a strategy for reducing cancer incidence, although associated side effects and in particular cardiovascular (CVS) side effects prevented their routine use in the general population.

In the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) study, 1,561 patients from 107 sites in 32 countries were recruited. Celecoxib reduced adenoma recurrence by a third after one and three years ($p < 0.001$). Celecoxib was particularly potent in inhibiting the recurrence of advanced adenoma by 51 % (Arber et al. 2006). The Adenoma Prevention with Celecoxib (APC) trial enrolled 2,035 patients that were randomized to receive placebo, celecoxib 200 or 400 mg bid. In patients taking celecoxib, polyp recurrence was reduced by 33 and 45 % for patients taking 400 and 800 mg of the drug, respectively ($p < 0.0001$). The relative risk of advanced adenomas was even more drastically reduced: by 57 and 66 %, respectively ($p < 0.0001$) (Bertagnolli et al. 2006). It was shown that compared to placebo, patients taking celecoxib had fewer and smaller adenomas as well as reduction in overall tumor burden. In a third study the Adenomatous Polyp Prevention on Vioxx (APPROVe), 2,547 participants were randomized to receive rofecoxib at 25 mg qd or placebo. A 25 % reduction in polyp recurrence was seen after one and three years, the effect on advanced adenoma was almost identical (RR-0.76 (95 % CI 0.69–0.83)) (Lagaos 2006).

However, all three studies were terminated earlier than planned due to substantial concern of increased cardiovascular system (CVS) toxicity, as seen by an increase in cardiovascular events (Bertagnolli et al. 2009; Bresalier et al. 2005). The CVS toxicity seen in the APPROVe trial prompted Merck to withdraw rofecoxib from the market; this decision was made even before the efficacy of the drug was evaluated. In the APC trial, the CVS toxicity, as evaluated by an independent cardiovascular adjudicating committee, increased from 1.0 % ($n = 7/679$) for placebo to 2.5 % ($n = 16/685$), and 3.4 % for celecoxib (200 and 400 mg bid, respectively) ($p < 0.01$). As a result, the NCI to suspended the trial. Lastly, 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) ($p = \text{NS}$).

The CVS toxicity persisted 1 year after rofecoxib was discontinued (APPROVe) (Lagaos 2006) and 2 years after celecoxib was discontinued (PreSAP and APC) (Bertagnolli et al. 2006; Arber et al. 2006) trials. Of note is the disparity in CVS toxicity from celecoxib between the APC and PreSAP trials (Arber 2008). A plausible explanation for this discrepancy is the difference in dosages. The APC trial gave celecoxib twice daily, for a total daily dose of 400 or 800 mg. It stands to reason that a greater dose increases the likelihood of an adverse reaction. Another plausible explanation for the discrepancy is that the 400 mg given once daily in the PreSAP trial was less toxic than the 200 mg given twice daily in the APC trial because of the relatively short half-life of celecoxib.

The actual extent of the CVS risk associated with COX-2 selective inhibitors remains unclear (Arber 2008). The trials were not designed to assess for cardiovascular events and it was difficult to control for confounding variables. Most importantly, the number of events was very low, and the vast majority of patients tolerated celecoxib without the related toxicity throughout the study (Bertagnolli 2007). The polyp recurrence rate reduction was the same after one and three years in all three studies. Cardiovascular toxicity started to increase only after 12–18 months. This suggests the possibility that use of COX-2 inhibitors for 1 year may be sufficient to prevent polyp recurrence, before toxicity appears. The gastrointestinal toxicity of celecoxib in the PreSAP and APC trials has also been recently adjudicated (Arber et al. 2011). There was no significant difference between the drug and placebo for the entire 3 year duration of the study. The discovery of CVS toxicity related to COX-2 specific inhibitors has made the development of new agents in this field difficult. However, to ignore potential benefit from chemoprevention is to accept a higher than necessary death rate from CRC.

The exact mechanism by which COX-2 inhibitors exert their anticancer properties is currently unknown. As mentioned above, the involvement of COX-2 in CR tumorigenesis has been attributed to its role in the production of PGE_2 which its levels were found elevated in CR cancers. Thus, deregulation of the COX-2/PGE_2 pathway appears to affect CR tumorigenesis via a number of distinct mechanisms involving promotion of tumor maintenance and progression, induction of metastatic spread, and others (Greenhough et al. 2009). There are at least seven mechanisms underlying the pro-tumorigenic effects of COX-2; (Tuynman 2004):

1. Inhibition of apoptosis
2. Increase of proliferation
3. Stimulation of angiogenesis
4. Induction of invasiveness
5. Modulation of inflammation
6. Conversion of carcinogens
7. Suppression of the immune system.

COX-2 inhibitors can also act through COX-2-independent pathways. They can induce apoptosis in cancer cells not expressing the COX-2 enzyme. A variety of non-COX-2 targets for COX-2 inhibitors have been suggested, such as, NF-kB,

peroxisome proliferator activating receptor -δ and -γ, protein kinase G, and Bcl-XL (Grover et al. 2003; Rao and Reddy 2004; Sinicrope 2006; Arber and Levin 2008).

Personalized medicine has remained an elusive goal and its utilization in chemoprevention is greatly anticipated. If COX-2 inhibition is the principal mechanism through which NSAIDs work, then these agents should be targeted at tumors that overexpress COX-2. Previous studies have shown that aspirin reduces the risk of CRC in COX-2 expressing cancers, but is not effective in COX-2 negative cancers (Chan et al. 2007). The efficacy and toxicity of COX-2 inhibitors may be affected by polymorphisms in COX-2, COX-2 targets, and related metabolizing enzymes (Arber 2008; Ulrich and Bigler 2006). It was suggested that polymorphisms in, COX-2 itself and metabolizing enzymes such as, uridine diphosphatidyl glucotransferase, may increase chemopreventive efficacy by up to 50 % (Macarthur et al. 2005; Lin et al. 2002). Moreover, polymorphisms in COX-2, and particularly -1195A > G may modulate the genetic susceptibility for CRC onset in some cases (Pereira et al. 2010). Another COX-2 polymorphism (rs4648319) was found to modify the effect of aspirin, supporting a role for COX-2 in the etiology of CRC and as a possible target for aspirin chemoprevention (Barry et al. 2009). It appears that polymorphisms in COX-2 targets or metabolizing enzymes may affect COX-2 efficacy and/or toxicity. However, the current literature on these interactions is still very limited (e.g., COX1 P17L or COX2 -765G > C). Reliable detection of gene-COX-2 interactions will require greater sample sizes, consistent definitions of COX-2 use, and evaluation of the outcome of chemoprevention studies. Nevertheless, these studies suggest that this genetically based higher-risk group definition may help to shift the balance between risk and benefits for the use of COX-2 inhibitors in chemoprevention that is currently hampered by adverse side effects (Pereira et al. 2010).

Obviously, the entire picture should be put in place, e.g. overall well-being, morbidity, and mortality. For example, the risk–benefit balance of aspirin for CRC prevention should be carefully weighted in conjunction with its ability to prevent other cancers, its well-established benefits in vascular disease, as well as its potential positive effects in subjects at high risk for Alzheimer disease (Agarwal et al. 1999; Reddy et al. 2006). All of these make aspirin an attractive candidate for personalized medicine.

Modern medicine favors combinatorial therapy. The goal being to increase efficacy, which tends to be modest with single compounds, while minimizing toxicity, by combining low doses of different agents. In rats with carcinogen-induced aberrant crypt foci, a combination of sulindac and statin significantly reduced the number of aberrant crypt foci to a greater degree than each of the drugs alone (Mamdani et al. 2004; Meyskens et al. 2008). The combination of the turmeric extract, curcumin, with low doses of celecoxib (2–5 μM) potentiates the growth inhibitory effect of either drug alone. 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) (Zell et al. 2009).

The study by Meyskens and colleagues represents the first clinical validation concept of using more than one drug for effective chemoprevention (Etminan et al.

2003). The authors have clearly shown that unwanted adverse effects can be prevented by using low doses of difluoromethylornithine (DFMO)- 500 mg and sulindac- 150 mg once daily, for 36 months in 375 patients with history of resected (≥3 mm) adenomas. The recurrence of one or more adenomas was 41.1 % in the placebo arm and 12.3 % in the treatment arm (RR, 0.30; 95 % CI, 0.18–0.49; $P < 0.001$). Advanced adenoma was seen in 8.5 or 0.7 % of the patients, respectively (RR, 0.085; 95 % CI, 0.011–0.65; $p < 0.001$. Serious adverse events (grade ≥3) occurred in 8.2 % of patients in the placebo group, and 11 % in the active intervention group ($p = 0.35$) (Etminan et al. 2003). In a later study, Meyskens et al. demonstrated that a high cardiovascular risk score at baseline may confer an increased risk of CVS events associated with DFMO treatment combined with sulindac, and a low baseline score may not increase this risk (Bond et al. 2010).

When contemplating the use of COX-2 inhibitors, six issues to consider include:

1. Moderate (personal or family history of colorectal neoplasia) to high-risk for CRC (FAP or HNPCC subjects)
2. Low cardiovascular risk patients
3. Non-high gastrointestinal risk patients
4. COX-2 expressing tumors
5. Polymorphisms in COX-2 targets and metabolizing enzymes
6. In the appropriate sub-group of patients with high cardiovascular risk and low gastrointestinal risk, celecoxib may be combined with low dose aspirin

In some subjects polyp recurrence occurred despite optimal colonoscopic surveillance. In the PreSAP, APC, and APPROVe studies adenomas were detected in patients that underwent up to four colonoscopies during a 5-year period, emphasizing the point that a strategy that relies on surveillance colonoscopies may not be sufficient in high-risk subjects. Further studies are needed to determine the incremental benefit that is provided with the addition of an effective chemopreventive agent. In these trials, patients who developed adenomas despite treatment with a chemopreventive agent had fewer and smaller adenomas than those who consumed placebo (Jaffe 1974; Grover et al. 2003; Baron et al. 2006). There is over all consensuses that removal of adenomas can prevent CRC by 80–90 %. Immense resources are investing therefore, in screening colonoscopy. Recently, this paradigm was challenged. While there is firm evidence that colonoscopy can prevent distal CRC, some concerns were raised regarding it is efficacy in preventing proximal CRC. Screening alone may not be sufficient to prevent the disease, even if it is fully implemented, suggesting that combining screening colonoscopy with chemopreventive agents might be the approach to eradicate CRC. Because small tubular adenomas are unlikely to progress to malignancy; these data suggest that addition of celecoxib to a surveillance regimen can be a very effective strategy.

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

It is now clinically possible to minimize adverse effects of chemotherapeutic and chemopreventive drugs by implementing combinatorial treatment strategies that will act synergistically. Nonetheless, the entire field of cancer prevention still suffers from neglect, as most efforts are dedicated to seeking optimal therapy of advanced disease. Combinatorial strategies represent a new approach that will counterbalance between cancer prevention and therapeutic approaches.

Whenever we aim for cancer prevention, and in particular in healthy individuals, one must carefully assess the benefit:risk ratio. The profile of efficacy and safety for any given indication varies significantly among subjects. It depends on the severity of the disease on one hand and the tolerance of the individuals receiving the drug on the other hand.

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