Pharmacological Prevention of Colorectal Cancer

Colorectal cancer (CRC) is a prevalent cause of morbidity and mortality in the western world. CRC carcinogenesis is a multi-step process that spans over many years providing an opportunity for intervention and cancer prevention. 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.

Pharmacoprevention refers to suppression or reversal of the carcinogenic process using a variety of pharmacological agents. Recent preclinical as well as clinical trials have provided data on the potential benefit of a number of elements in the prevention setting. In this review we will focus on the main pharmacological agents studied in the chemopreventive setting. We will discuss the use of Non-Steroidal Anti-inflammatory drugs (NSAIDs) including coxibs as well as a new group of agents the NO-NSAIDs. HMG-CoA reductase inhibitors, ursodeoxycholic acid, Difluromethaylornitine (DMFO), and hormone replacement therapy that all have chemopreventive potential will also be discussed.

At present, the only approved drug for chemoprevention of CRC is celecoxib and only for high-risk patients with Familial Adenomatous Polyposis (FAP). This is mainly due to cardiovascular toxicity recently reported in the patients with h/o sporadic adenomas. Aspirin and sulindac have also repeatedly demonstrated efficacy in this setting. However, due to increased risk of GI toxicity associated with their benefit has to be weighed against their risk.

(continued on page 23)
INTRODUCTION

Colorectal cancer (CRC) is a prevalent cause of cancer related death in the United States. An estimated 149,000 new cases are expected to be diagnosed in 2006 and 55,000-related deaths will occur (1,2). In women, CRC ranks third after lung and breast cancer, and in men, it ranks third after lung and prostate cancer (1). The incidence of CRC increases sharply after the age of 50 and the estimated lifetime risk is 5% to 6%. Approximately 75% of new cases occur in individuals at average risk (3, 4). Strategies to improve survival and reduce mortality from this disease focus on prevention, early detection and improvement of current therapy. Survival is directly related to the stage of the disease at the time of diagnosis. CRC screening and surveillance strategies for early detection of disease are a critical component of CRC prevention and are standard clinical practice. However, their impact is limited due to low compliance with current guidelines. CRC has a natural history of transition from a precursor lesion, i.e. adenomatous polyp to cancer that spans, on average, 15 years providing an extended opportunity for intervention and cancer prevention.

By the age of seventy, 50% of individuals will have an adenomatous polyp (5). The risk of cancer within these polyps is linked to size, villous histology, and the degree of dysplasia. Removal of adenomas at colonoscopy has been shown to significantly reduce CRC incidence (6). Even with polyp removal, studies indicate an adenoma recurrence rate of 30% to 42% three years later (6). Adenomas help identify a subset of the population that is at increased risk of harboring and developing cancer. Science and technology have evolved to a point where we are able to use our knowledge of cancer biology to identify individuals at increased risk and interrupt the process of malignant transformation at the level of the pre-cancerous lesion.

RISK STRATIFICATION

While subjects in the general population are considered to be at average risk for CRC, patients with prior adenomas or CRC and those with a history of inflammatory bowel disease are at increased risk. The highest known risk groups include two familial syndromes, i.e., familial adenomatous polyposis (FAP) and HNPPC. Germline mutations in the APC gene are responsible for FAP and, without colectomy, essentially all patients will develop CRC. HNPPC patients show inherited mutations in DNA mismatch repair genes, develop early onset CRC with frequent synchronous tumors and extracolonic cancers, and display a phenotype outlined above for sporadic CRCs with MSI (7). These patients have an 70%–80% approximate lifetime risk of CRC. Collectively, these two hereditary syndromes account for less than 5% of all new cases of CRC (8).

Chemoprevention involves the long-term use of nutritional or pharmacological agents that can delay, prevent or even reverse this process.

The ideal chemopreventive agent should fulfill a number of criteria:
1. Should be effective
2. Have a convenient dosing schedule, preferably daily
3. Minimal side effects or a low but acceptable profile in high-risk populations
4. It should be easily administered
5. It should have a low cost

Recent preclinical as well as clinical trials have provided data on the potential benefit of a number of nutritional and pharmacological elements in the chemoprevention setting. In this review we will focus on the pharmacological agents studied in the chemopreventive setting. The groups of drugs that have triggered most attention are the various Non- Steroidal Anti Inflammatory Drugs (NSAIDs). Interest in these agents is based on a strong association with reduced CRC risk in observational studies, preclinical animal models, and the link between chronic inflammation and cancer. Cyclooxygenase (COX) is the best-defined molecular target of NSAIDs. The constitutive COX-1 isoform is a “housekeeping” gene involved in the maintenance of normal tissue homeostasis. COX-2 is an inducible enzyme that is up-regulated at sites of inflammation (9) and is overexpressed in 80% of human CRCs and in 40% of colorectal adenomas relative to normal mucosa (10,11). Traditional NSAIDs inhibit the activity of both COX-1 and COX-2 isoforms. Gastric mucosal injury, renal toxicity, and the
anti-platelet effects of NSAIDs are believed to be mediated by inhibition of COX-1 and prostaglandin synthesis (12). Since COX-2 is induced at sites of inflammation, the anti-inflammatory and analgesic properties of NSAIDs are attributed to their ability to inhibit COX-2. The best evidence supporting the role of COX-2 in intestinal tumorigenesis was shown in genetically manipulated murine models of FAP, where deletion of the COX-2 gene in APCdelta716 mice was found to significantly reduce the number of intestinal polyps in double knockout mice relative to COX-2 wild-type animals (13).

While the exact mechanism(s) by which NSAIDs exert their anti-tumor effects remain incompletely understood, potential mechanisms may include stimulation of new blood vessels (angiogenesis), inhibition of programmed cell death (apoptosis), regulation of cellular adhesion, and increased tumor cell invasiveness (14). Both COX-dependent and COX-independent effects of NSAIDs have been described (15–17).

Epidemiologic studies have consistently shown a 40%–50% reduction in CRC incidence among chronic users of NSAIDs (18–20). These studies (18–22) suggest that aspirin and other NSAIDs may prevent CRC. The magnitude of risk reduction across studies is reassuringly consistent as is the demonstrated need for frequent, continued use. In the Nurses’ Health Study (23) women who used aspirin two or more times per week were 25% less likely to develop adenomas than were women who took aspirin less often. However (24), a secondary analysis from the Women’s Health Initiative study evaluated 91,574 participants who were followed annually for incident CRC cases over six years. There was no significant association between any aspirin use and risk of colorectal cancer (hazard ratio = 0.96, 95% confidence interval: 0.8, 1.2) (24).

The clinical utility of NSAIDs for chemoprevention in individuals with FAP was initially observed in 1989 when a decrease in adenomatous polyps was found in a small series of patients with Gardner’s syndrome, who were using sulindac (25). Subsequent controlled trials evaluating sulindac for the treatment of polyps in FAP patients demonstrated the effectiveness of this agent in both polyp prevention and regression. However, the effect of sulindac treatment was incomplete in that not all polyps regressed and polyph growth was observed three months after the drug was discontinued (26). While sulindac can regress existing polyps in patients with FAP, sulindac (75 or 150 mg twice a day) taken for four years failed to significantly reduce the mean number or size of polyps when compared to placebo in 41 genotype-positive, phenotype-negative FAP subjects (27). Thus, this agent failed in primary prevention of colorectal polyps in this population. In a double blind, randomized-controlled trial, a 28% reduction in the mean number of colorectal polyps (p = 0.003 for comparison with placebo) was demonstrated in 83 patients with FAP treated with high-dose celecoxib, a selective COX-2 inhibitor, at a dose of 400 mg twice daily for six months (28). No differences in side effects were found between subjects receiving celecoxib and those receiving placebo. Based upon this study, the Food and Drug Administration approved celecoxib for use in the reduction of adenomatous polyps as an adjunct to usual care in patients with FAP. We emphasize that surgery remains the mainstay of FAP management and that celecoxib or sulindac treatment is not a substitute for surgery. Potential benefits of the adjunctive use of these agents include delaying colectomy in selected young adult patients with FAP, or the potential to lengthen the endoscopic surveillance intervals in FAP patients with ileo-rectal anastomoses and an intact rectum.

In the sporadic setting, in patients with history of CRC, Sandler, et al (29), reported one or more adenomas in 17% of aspirin users compared to 27% of placebo users (p = 0.004, HR 0.64) after a median treatment time of 31 months. Based upon these data, the study was terminated prematurely due to activation of an early stopping rule. In another study, Baron, et al (30) randomly assigned patients with a history of adenomas to placebo, 81 mg of aspirin or 325 mg of aspirin. The incidence of one or more adenomas was 47% in the placebo group, 38% in the group taking 81mg aspirin (RR 0.81, 0.69–0.96) and 45% in the 325 mg aspirin group (RR 0.96, 0.81–1.13) after a median treatment time of 33 months. While the 81 mg aspirin dose was efficacious, it is unclear why the higher 325 mg dose of aspirin did not significantly reduce the risk of adenoma recurrence in this trial. In addition, seven

(continued on page 26)
non-hemorrhagic strokes were observed in the aspirin-treated cohorts: two with lower-dose ASA and five with higher-dose ASA. In another similar trial, 272 patients with prior adenomas were randomly assigned to daily aspirin (160 or 300 mg/day) or placebo (31). In this study, aspirin use was associated with a 27% reduction in the risk of recurrent adenomas at one year colonoscopy (RR 0.73(0.52–1.04)).

While studies show that aspirin has a protective effect in reducing polyp recurrence, we must realize the limitations of these studies that include inadequate follow-up, inconsistent results based upon aspirin dose, and the potential for adverse events, particularly gastrointestinal bleeding and hemorrhagic stroke, even at low doses. Studies so far have not shown that aspirin is cost effective for CRC prevention, largely due to costs associated with treatment-related complications (32,33). For the mean time, aspirin should not be recommended for the chemoprevention of sporadic adenomas. Aspirin could have an important influence as it has the potential to decrease polyp size and number and has been shown to delay polyp development leading to a reduction in surveillance intervals. Aspirin therapy, presently, does not eliminate the need for colonoscopy and the added clinical benefit of its use in the context of surveillance colonoscopy will have to be proven in clinical randomized trials.

**COXIBs**

Selective COX-2 inhibitors, i.e., coxibs, were developed to reduce the toxic effects related to COX-1 inhibition including gastroduodenal mucosal ulceration, renal toxicity, and platelet dysfunction. However, recent chemoprevention studies evaluating coxibs have identified significant cardiovascular toxicities. Three multi-center, prospective and placebo-controlled trials were conducted in the US and Europe to evaluate the efficacy of rofecoxib or celecoxib for the pharmacoprevention of sporadic adenoma recurrence. Taken together, all three trials found that selective COX-2 inhibitors can significantly reduce sporadic polyp recurrence rates at one and three years (34-36). However, in the recently published APPROVe (36) and the APC (34) trials, rofecoxib and celecoxib were associated with a significant increased risk of cardiovascular events, mainly myocardial infarction, stroke, and heart failure. Due to these reports Merek Inc. (manufacturer of Vioxx), announced the early termination of their study and withdrew the drug from the market. In the treatment group, a total of 47 (3.7%) subjects taking rofecoxib had a confirmed thrombotic event compared with 27 (2.1%) patients in the placebo group (RR: 1.89 p = 0.008) (36, 37). Later on, the APC trial was terminated early by the National Cancer Institute due to analysis by an independent adjudication cardiovascular committee. There analysis found a significant and dose-related excess of major cardiovascular events for the celecoxib 200 (RR 2.6, 95% CI 1.1–6.1) and 400 mg bid (RR 3.4 CI 95% 1.5–7.9) groups, respectively compared to the placebo group (38, 39). In the PreSAP trial, comparison of cardiovascular events between the celecoxib 400 mg qd group and the placebo group was not significant (35). Discrepant results for cardiovascular outcomes in the APC and PreSAP studies were further addressed by combining both study populations. Combined data from the APC and PreSAP studied yielded 83 patients that experienced a major cardiovascular event. Celecoxib at 200 or 400 mg twice daily or 400 once daily showed a nearly 2-fold increased cardiovascular risk. However, a trend toward a dose-dependent increase in cardiovascular events and hypertension, suggests that lower doses or other dose intervals may be associated with less risk (39).

The message of these trials is loud and clear. A proof of concept was demonstrated. CRC can be prevented by pharmacological intervention. Selective COX-2 inhibitors are highly effective agents for prevention of pre-cancerous lesions of the colon. Although COXIBs are relatively safe in terms of GI toxicity, their use in the setting of CRC prevention carries a risk of serious cardiovascular complications. This is only the first line of therapy. Obviously, we need a better selection of patients and improved drugs, or combination of drugs. There is a need to identify those subjects at high risk for CRC, and low risk for CVS toxicity. The goal of future studies is to develop ways of blocking COX-2 activities without disrupting the cardiovascular system.
Other pharmacological agents that have been studied for use in chemoprevention are the NO-NSAIDs, HMG-CoA reductase inhibitors, Ursodeoxycholic acid (UDCA), Difluromethylnitirine (DFMO), and hormone replacement therapy. While none of these are recommended for routine clinical use, their future remains to be determined.

**NO-NSAIDS**

NO-NSAIDs are a novel group of hybrid nitric oxide-releasing NSAID that are currently under study. NO is recognized as a critical mediator of gastrointestinal mucosal defense, exerting many of the same actions as prostaglandins in the gastrointestinal tract (40). In experimental animal models linking a NO-releasing compound to a NSAIDS has been found to reduce the severity of gastric injury (41–43). In vivo studies have shown that NO-NSAIDs suppress the formation of azoxymethane-induced colonic aberrant crypt foci (44) and colon cancer (45). NO-aspirin has been shown to effectively reduce intestinal carcinogenesis in the Min mouse model (46). This group of drugs is currently being evaluated in clinical trials.

**STATINS**

A therapeutic group of drugs that inhibit the hepatic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol synthesis. Statins that were originally approved to prevent cardiovascular disease have also been shown to modulate tumor cell growth and induce apoptosis. In vitro studies have shown that low dose lovastatin potentiates sulindac's chemopreventive effects (47,48). In an animal model of carcinogen induced colon cancer, statins significantly reduced the number of colonic neoplasia (49). In humans, two large trials of simvastatin and pravastatin in patients with coronary artery disease found a reduction in colon cancer incidence (50,51). Furthermore, a recent case control study that analyzed 1,953 patients with colon cancer and 2,015 controls found that the use of statins for five years was associated with a 47% relative reduction in the risk of CRC after adjustment for other known risk factors (use of NSAIDs, family history, physical activity, and ethnicity) (52). Statins have been shown to be associated with a tolerable adverse effect profile in patients with hypercholesterolemia but their toxicity in patients without hyperlipidemia needs to be addressed. Furthermore, their overall benefit in preventing colon cancer requires further studies before final conclusions can be drawn.

**URSODEOXYCHOLIC ACID**

Ursodeoxycholic acid (UDCA) is used in the treatment of primary biliary cirrhosis as well as the medical dissolution of gallstones. UDCA acts as a chemopreventive agent by reducing the colonic concentration of deoxycholic acid, which is cytotoxic to colonic epithelial cells and induces hyper-proliferation by blocking two separate neoplastic pathways (modulating protein kinase C and phospholipase A2 expression). In addition it is an antioxidant that stabilizes the mitochondrial membrane thereby preventing oxidative injury to DNA. Numerous studies have shown the chemopreventive effects of UDCA in rat models of carcinogenesis (53,54) and the results of human studies are now beginning to emerge (55).

**DIFLUROMETHYLNITRINE**

Difluromethylnitirine (DFMO) is an irreversible inhibitor of ornitine decarboxilase (ODC), the first and rate-limiting enzyme in the polyamine synthesis. Somatic cells in the majority of colorectal polyps and cancers contain mutations/deletions in the adenomatous polyposis coli (APC) tumor suppressor gene. APC influences expression of ODC in that loss of APC function leads to alterations in ODC. The polyamine pathway appears to have an essential role in CRC development (55). ODC and polyamines have been found to be elevated in adenomatous polyps and CRCs relative to normal mucosa (56,57). Due to ototoxicity, DFMO is under investigation as a chemopreventive agent at low doses mainly in conjunction with NSAIDs (to be discussed later).

**HORMONE REPLACEMENT THERAPY (HRT)**

During the past 20 years, CRC mortality has decreased only slightly in men but more in women. In most stud-
ies, women who use postmenopausal hormones have an approximately 30% to 40% decreased risk of CRC. The effect is stronger in women who received continuous hormone therapy for more than 11 years. While the mechanism underlying this protective effect is unclear, estrogen may prevent CRC by decreasing the production of secondary bile acids, by decreasing the production of insulin-like growth factor 1, or by exerting a direct effect on the epithelium and perhaps by a combination of these mechanisms (58–60). The Women’s Health Initiative HRT estrogen plus progestin and estrogen-only arms are part of a large NIH-sponsored randomized controlled trial. In the estrogen plus progestin arm of this study, a 37% reduction in CRC incidence was found. However, this arm detected increased incidences of cardiovascular events and breast cancer, and both arms showed an increased rate of thromboembolic events and stroke (61). Due to these findings HRT is not recommended for use as a chemopreventive agent.

COMBINATION TREATMENT

Many agents have been studied in the chemopreventive field. Although some show potential benefits, their chemopreventive efficacy in clinical trials has been modest and/or they have an unacceptable toxicity profile. Combining low doses of different agents has the possible advantage of increasing their efficacy while minimizing toxicity. The combination of lovastatin and sulindac has been studied in animal models of carcinogen-induced aberrant crypt foci (ACFs), thought to be precursors of adenomas. A higher reduction in the number of ACFs was reported in rats receiving both agents, as compared to each of the drugs alone (48). Similar results were reported when atorvastatin, celecoxib, and aspirin, were studied in a colon cancer animal model. Again, low doses of these agents, combined, inhibited colon carcinogenesis more effectively than each of the drugs alone given at a higher dose (62). In another study the combination of piroxicam and DFMO was much more effective than either agent alone and resulted in a significant number of mice totally free of any intestinal adenomas (P < 0.001), in contrast to the 100% incidence and high multiplicity in control Min mice model (63). In this model, combining ursodeoxycholic acid and sulindac was more effective than either alone in prevention of colonic tumors (64). Due to these impressive results in the preclinical setting, combination treatment is currently undergoing extensive study in the chemopreventive field. In the sporadic setting, DFMO is being studied in combination with sulindac in a phase III study in patients with a history of adenomas.

Chemoprevention trials are an enormous expense and a major challenge to drug development companies. These studies require a large patient number and many years of treatment to reach the end point (i.e. adenoma or cancer). In this regard, much more time is required to produce the evidence necessary to approve a drug for marketing. The recent data regarding the toxicity of the COXIBs has taught us that providing a drug for extended periods of time is unpredictable and can lead to discontinuation of drugs that millions of dollars have been invested in their development. Basic research is required to guide a better selection of drugs for further study and to determine ideal intermediate surrogate markers.

At present, the only approved drug for chemoprevention of CRC is celecoxib and only for high-risk patients with FAP. Aspirin and sulindac have also repeatedly demonstrated efficacy in this setting. However, due to the increased risk of GI toxicity associated with these medications, their benefit will have to be weighed against their risk. FAP patients represent a population with greater morbidity and a 100% lifelong risk of CRC development. They are also usually younger subjects with a minimal cardiovascular risk. Hence, they represent an ideal group to be treated with COX 2 inhibitors. Currently, chemopreventive treatment will have to be assessed on an individual basis and in the future, decisions will be greatly facilitated by better patient risk stratification and the hope for molecular tumor profiling.

Screening methods and surveillance are the standard of care for high-risk patients with history of CRC or adenomatous polyps and for the general population based on age. An important issue is whether chemoprevention can provide added benefit over colonoscopy and polypectomy and/or potentially reduce colonoscopic surveillance intervals. This unre-
solved issue is an important topic for future study and research and the answer remains to be determined in the future.

References
Pharmacological Prevention of Colorectal Cancer

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