Current Application of Selective COX-2 Inhibitors in Cancer Prevention and Treatment

Review Article [1] | May 01, 2002
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The multistep process of carcinogenesis, which can take many years, provides many opportunities for intervention to inhibit disease progression. Effective chemoprevention agents may reduce the risk of cancer by inhibiting the initiation stage of carcinoma through induction of apoptosis or DNA repair in cells harboring mutations, or they may act to prevent promotion of tumor growth. Similarly, chemoprevention may entail blocking cancer progression to an invasive phenotype.

Cyclooxygenases (COXs) are enzymes that catalyze the rate-limiting step in the conversion of arachidonic acid to prostaglandins (Figure 1).[1-3] Prostaglandins, along with other arachidonic acid products such as thromboxane and 15-hydroxy-eicosatetraenoic acids, belong to the eicosanoid family of fatty acid molecules, which are known to regulate many physiologic processes including the inflammatory response and other immune response modulators,[4-6] ovulation,[7,8] and mitogenesis.[9,10] Paradoxically, prostaglandins also have been shown to have anti-inflammatory and immunosuppressive effects. Studies conducted by Gualde and colleagues demonstrated that prostaglandins inhibited T-cell proliferation in vitro.[11] Furthermore, prostaglandins can block production of cytokines by T lymphocytes.[12]

Synthesis of prostaglandins can be regulated at several different points in the pathway (Figure 1). In the first step, membrane phospholipid is converted to arachidonic acid via phospholipase A\textsubscript{2}. Subsequently, arachidonic acid is converted to prostaglandin H\textsubscript{2} through a two-step process that involves COX activity to convert arachidonic acid to prostaglandin G\textsubscript{2}, followed by a peroxidase reaction that is also catalyzed by COX to produce prostaglandin H\textsubscript{2}.[13-15]

The COX enzyme family comprises two known isoforms, COX-1 and COX-2. Cyclooxygenase-1 is a membrane-bound hemoglycoprotein that is constitutively expressed in the endoplasmic reticulum of cells in most healthy tissues and is responsible for local prostaglandin synthesis. In contrast, COX-2 is primarily an inducible COX isoform, although low basal expression is apparent in some tissues, including brain and kidney.[16,17] There are a number of structural differences between the COX-1 and COX-2 genes, including differences in the cis elements within the promoter regions and 3´-untranslated domains.

The structure of the COX-2 gene suggests that it is an immediate, early gene product that can be switched on rapidly during the inflammatory response.[18,19] Cyclooxygenase-2 synthesis is inducible by a variety of stimuli, including proinflammatory cytokines such as interleukin-1 alpha and beta,[20,21] growth factors such as platelet-derived growth factor[22,23] and epidermal growth factor,[24,25] and lipopolysaccharide and endothelin.[26,27]

**COX-2 Inhibitors and Cancer**

Most nonsteroidal anti-inflammatory drugs (NSAIDs) that are commonly administered to patients inhibit both COX-1 and COX-2. However, inhibition of the inducible isoform, COX-2, is the primary anti-inflammatory mechanism.[5,28,29] Adverse effects associated with long-term use of NSAIDs, including gastritis and gastrointestinal ulceration, in addition to reversible liver and kidney dysfunction, are thought to be primarily due to inhibition of the constitutively expressed COX-1 isoform.[30-32] In recent years, COX-2-specific NSAIDs, including celecoxib (Celebrex) and rofecoxib (Vioxx), have become available. Selective COX-2 inhibitors are advantageous because they may inhibit pain and the inflammation process in arthritis and oncogenesis. However, they do not inhibit COX-1 enzymes, the products of the “housekeeping genes” required for the maintenance of the gastrointestinal tract and for normal renal and hepatic function.
Rigas and colleagues have demonstrated that colorectal adenomas and adenocarcinomas express elevated levels of prostaglandins.[33] Furthermore, accumulation of prostaglandins is associated with increased expression of COX-2, but not of COX-1.[34] It is also known that prostanooid levels increase during the progression from adenoma to adenocarcinoma in patients with familial adenomatous polyposis.[35] In addition, elevated prostanooid expression is associated with tumor growth, metastatic potential,[36] disease stage,[37] recurrence,[38] and survival[39] in a broad spectrum of tumor types. Furthermore, overexpression of COX-2 in humans has been documented in many cancer types and neoplastic precursor lesions (Table 1).[40-81]

These data indicate that selective inhibition of COX-2 may be an effective strategy for preventing colorectal cancer and also may have application in other cancers. Furthermore, because COX-2 overexpression has been observed in both preneoplastic lesions and cancers, chemoprevention intervention is possible at multiple stages of carcinogenesis.

Overexpression of COX-2 may affect a broad range of mechanisms implicated in the process of carcinogenesis, including angiogenesis, apoptosis, and immune function. Cancer prevention offers more than one opportunity to inhibit disease growth. Effective chemopreventive agents may reduce the risk of cancer by preventing the initiation stage of carcinoma by inducing apoptosis or DNA repair in cells harboring mutations, or they may act to prevent tumor growth during the promotion and progression stages of carcinogenesis (Figure 2). Ongoing clinical trials evaluating COX-nonspecific and COX-2-specific inhibitors as chemoprevention and therapeutic agents are shown in Table 2[82-84] and are discussed in the following sections.

Colorectal Cancer

Colorectal cancer is a major national health problem. It is the third leading cause of cancer death in the United States, with 2002 estimates of 148,300 new cases and 56,600 deaths.[85] Some (approximately 15%) individuals who develop colorectal carcinoma belong to clinically identifiable high-risk groups due to familial adenomatous polyposis and hereditary nonpolyposis syndromes.[86] However, the majority of cases of colon carcinoma develop sporadically in patients who have no known predisposition for the disease.[87] It is estimated that adherence to the current American Cancer Society and Gastrointestinal Society colorectal cancer screening guidelines could lower the annual mortality rate by at least 50% over the next decade.[88]

COX-2: Expression and Preclinical Data

In humans, overexpression of COX-2 has been documented in colorectal adenomas and cancers, but not in normal-appearing mucosa.[89] For example, Figure 3 shows immunohistochemical staining for COX-2 in colon adenoma tissue. Similar overexpression of COX-2 has been documented in a wide range of cancers and their precursors (Table 1).[40-81] The chemopreventive effects of COX-2 inhibitors on the development of colorectal cancer are the subject of intense study, and animal models have been useful in investigating colorectal cancer pathogenesis.

A mutation in the adenomatous polyposis coli (APC) gene results in spontaneous adenoma formation in the small intestine of APC delta716 knockout mice. Using this rodent model, Oshima and colleagues demonstrated that there is a cause-effect relationship between COX-2 overexpression and gastrointestinal tumor incidence.[90] It was shown that suppression of one allele of the COX-2 gene reduced the number of intestinal polyps by 66%, and suppression of both alleles resulted in a reduction of 86%.[91] Furthermore, treatment of COX-2-expressing azoxymethane-treated rats with oral celecoxib suppressed formation of colorectal tumors by > 90%, compared with a suppression of 40% to 65% following administration of a nonselective COX inhibitor.[91,92]

Reduced Incidence of Colorectal Neoplasia

In prospective cohort studies, long-term administration of aspirin and other NSAIDs has been associated with a reduction in the incidence of colorectal adenomas, cancer, and cancer mortality by 40% to 50%.[93-95] An inverse relationship also has been demonstrated between the use of NSAIDs and the incidence of colorectal cancer in several case studies.[96,97] Furthermore, clinical trials
showed that the administration of sulindac, a commonly prescribed NSAID, prescribed to familial adenomatous polyposis patients was associated with a reduction in the number and size of adenomas.[97-99]

The US Food and Drug Administration recently granted approval of celecoxib for treatment of familial adenomatous polyposis. Celecoxib, which was initially approved for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis, is highly selective for COX-2[100] (375-fold greater selectively compared with COX-1) and has a significantly reduced incidence of common gastrointestinal toxicities, such as bleeding and upper gastrointestinal ulcers, associated with NSAIDs.[101]

The pivotal trials of celecoxib for the treatment of familial adenomatous polyposis enrolled 77 patients who were randomized to receive either placebo or celecoxib (100 or 400 mg twice daily) for 6 months.[102] The primary efficacy end point was the percent change in the number of colorectal adenomas (> 2 mm in size) at 6 months. There was a 4.5% reduction in the placebo-treated group, a 11.9% reduction in the 100-mg celecoxib-treated group, and a 28.0% reduction in the 400-mg celecoxib-treated group. The decrease in incidence between the 400-mg celecoxib twice-daily group and the placebo group was statistically significant (P = .003). The prevalence of adverse events was similar among the treatment groups and consisted primarily of diarrhea, dyspepsia, fatigue, upper respiratory infection, and rash.

The results from the pivotal trial of celecoxib in familial adenomatous polyposis support further investigation of COX-2 inhibitors for an overall chemoprevention strategy for colorectal tumors in other populations at risk, including patients with sporadic adenomatous polyps. As shown in Table 2,[82-84] there are several recently initiated clinical trials of celecoxib in the prevention or recurrence of colorectal adenomas. Two are being conducted under the sponsorship of the Division of Cancer Prevention at the National Cancer Institute.

One clinical trial is being led by Monica Bertagnolli, MD, Brigham and Women’s Hospital, Dana-Farber Cancer Institute, Boston. This trial is investigating two dose levels of celecoxib compared with placebo with 1- and 3-year colonoscopy end points. A second phase III clinical trial (using a factorial design) is studying celecoxib (400 mg/d) vs selenium (in the form of baker’s yeast) vs the combination of celecoxib/selenium vs a double placebo. This study is being conducted at the Arizona Cancer Center, Tucson, by Drs. David Alberts and Peter Lance.

An additional randomized, phase III trial is evaluating the potential for celecoxib to reduce the incidence of sporadic adenomas. Adenoma recurrence rates will be evaluated at a 3-year colonoscopy end point. The results of these trials will not be available for several years, but could establish COX-2 inhibitors as important components of the management strategy for colorectal adenomas and the prevention of colon cancer.

Nonmelanoma Skin Cancer

It is well recognized that chronic sun exposure is a major etiologic agent for skin cancer, contributing to over 1 million new cases of basal cell carcinoma and squamous cell carcinoma each year in the United States. Although the majority of skin cancers are basal cell carcinomas, which are relatively benign, squamous cell carcinomas account for approximately 2,000 deaths annually.[103] Ultraviolet (UV)-B exposure is responsible for most squamous cell skin cancers.[104-106] It is considered to be the principal carcinogen in skin cancers and is involved with all stages of carcinogenesis (initiation, promotion, and progression). Ultraviolet-A is also capable of causing oxidative stress and is also associated with UV-induced carcinogenesis, particularly melanoma.[106-108] Actinic keratosis is considered a precursor lesion of squamous cell carcinoma, with approximately 60% of squamous cell carcinomas evolving from actinic keratosis.[109,110]

COX-2: In Vitro and Preclinical Data

Several mechanisms for UV-induced skin carcinogenesis have been defined, including dysregulation of cell signal transduction pathways[111-113] and upregulation of COX-2 expression.[114,115] In the
normal epidermis, the balance between proliferation of cells in the basal layer, cell differentiation in the suprabasal spinous and granular layers, and apoptosis at the transitional zone (where the stratum granulosum and stratum corneum meet) is tightly regulated. Cells lose their proliferative capacity as they undergo terminal differentiation and leave the basal cell layer.

When homeostasis is maintained in the epidermis, COX-1 is constitutively expressed by keratinocytes and COX-2 is abnormally expressed.[116] Studies conducted by Athar and colleagues, however, have demonstrated that COX-2 is expressed in the epidermis in response to tumor promoting agents,[117] and other colleagues demonstrated that the differential expression of COX-2 in mouse skin carcinoma is regulated by cis elements within the promoter region of the COX-2 gene.[117,118] Neufang and colleagues showed that, in a transgenic mouse model, induced expression of COX-2 in the epidermis resulted in abnormal epidermal differentiation.[119] Furthermore, proliferation of epidermal cells was increased and, in some regions of the epidermis, there was an increase in the number of viable cornified layers.

Prostaglandins are actively synthesized by the human epidermis: COX-2-mediated overexpression of prostaglandin E$_2$ has been shown to increase epidermal cell proliferation in vitro.[114] Prostaglandins generated by the arachidonic acid cascade have been implicated in various models of skin tumorigenesis. Elevated levels of protaglandin E$_2$ have been observed in basal cell carcinoma, squamous cell carcinoma, and actinic keratosis. Data suggest that prostaglandin E$_2$ overexpression may correlate with the propensity for metastatic and invasive behavior.[120]

In the context of skin tumorigenesis, chemical carcinogenesis models have implicated COX-2-regulated prostaglandin expression in mediating tumor promotion.[121,122] Upregulation of COX-2-induced prostaglandin production causes an increase in cell growth and, as shown by Tsujii and DuBois, skin carcinoma cells overexpressing COX-2 are resistant to apoptosis.[60,123]

Cyclooxygenase-2 overexpression has also been demonstrated in UV-exposed human skin cells. Buckman and colleagues showed that exposure of human keratinocytes in vitro to UV-B caused a significant increase in expression of prostaglandin E$_2$.[124] In cultured human keratinocytes, UV-B-induced COX-2 activity was blocked completely by indomethacin, a nonspecific COX inhibitor, and by SC58125, a COX-2-specific inhibitor.[125]

**Clinical Data and Clinical Trials**

Kagoura and colleagues used immunohistochemistry to investigate COX-2 expression in basal cell carcinoma, Bowen's disease, squamous cell carcinoma, and metastatic tumors of the skin.[126] Four of 16 basal cell carcinoma cases tested positive for COX-2. In Bowen's disease, the staining intensity for COX-2 was greater than that observed in basal cell carcinoma.

In addition, 11 of 15 squamous cell carcinoma patients tested positive for COX-2. The pattern of staining was heterogeneous, with more intense staining in the centers of the tumor loci. In metastatic tumors, the percentage of COX-2-positive tumor cells and the intensity of staining was low compared with Bowen's disease and basal cell carcinoma, suggesting that COX-2 may play a greater role in the early stages of squamous cell carcinogenesis.

Currently, there are several ongoing clinical trials examining the effect of COX-2 inhibition on skin cancer ([Table 2]).[82-84] At the University of California, San Francisco, a study is being conducted to examine whether celecoxib prevents the development of basal cell carcinoma in patients with basal cell nevus syndrome. Celecoxib is also being tested in several ongoing, placebo-controlled clinical trials for preventing the development of new actinic keratosis lesions.

A phase IIb, double-blind, placebo-controlled trial is ongoing at the University of Alabama with sponsorship from the National Cancer Institute. The primary end point of this study will be inducing actinic keratosis regression. Secondary end points include the effect of celecoxib on potential surrogate end point biomarkers in areas of actinic keratosis, sun-exposed skin, and non-sun-exposed skin, and the correlation of these biomarkers with clinical outcome.

Reports examining COX-2 and skin carcinogenesis illustrate the need for evaluation of the efficacy of
COX-2-selective inhibitors as chemoprevention agents to inhibit the course of UV-induced skin cancer. Future research should combine in vitro techniques, and available transgenic knockout or overexpression mouse models, in addition to human studies, to more clearly define the role of COX-2 in UV-B- and UV-A-induced carcinogenesis of the skin.

**Lung Cancer**

Lung cancer is the leading cause of cancer deaths in the United States. Furthermore, lung cancer has a high propensity to spread by hematologic and lymphatic routes. More than 86% of cases occur in current or former smokers.[127,128] Approximately 75% of lung cancers are classified as non-small-cell lung carcinoma. The disease is usually diagnosed at an advanced stage when it is therapeutically intractable.[129,130] Clearly, understanding the biology of the disease and discovering specific molecular targets to facilitate early detection and treatment would be valuable.

**COX-2: In Vitro and Preclinical Data**

Over 30% of non-small-cell lung cancer tumors and cell lines harbor an activating mutation in the K-ras oncogene,[131] which appears associated with expression of COX-2 in a panel of non-small-cell lung cancer cell lines.[132] Several reports also have shown that NSAIDs block the transformed growth of non-small-cell lung cancers that express the K-ras mutation.[133-135] It has been hypothesized that the generation of bioactive lipids derived from the arachidonic acid metabolic pathway modulates physiologic and pathologic responses involved in tumor growth and tumor progression in the lung. This theory has been based on data indicating that COX inhibitors inhibit the growth of human lung cancer cell lines in vitro and in animal models,[136,137] and abnormalities in arachidonic acid metabolism are present in non-small-cell lung cancer.[138]

Masferrer and colleagues studied the effect of celecoxib in the Lewis lung model.[139] Mice were injected with cancer cells into the foot pad, then fed either a control diet or a diet supplemented with celecoxib. Over a period of 30 days, celecoxib caused a dose-dependent decrease in tumor volume and, at higher doses, celecoxib induced a decrease in the size and number of lung metastases. It was hypothesized that the decrease in tumor size and metastatic invasion was due to celecoxib-induced inhibition of angiogenic activity.[140]

**Clinical Data and Clinical Trials**

Epidemiologic studies have shown that NSAIDs, including aspirin, significantly reduce the risk of lung cancer.[41,42,141] Furthermore, COX-2 expression appears elevated in non-small-cell lung cancer,[131,132] and increased COX-2 expression is associated with poor prognosis.[43] Using in situ hybridization with a COX-2 antisense probe, Khuri and colleagues demonstrated that COX-2 expression in stage I disease was associated with decreased survival rates.[61]

Cyclooxygenase-2 is diffusely overexpressed in atypical adenomatous hyperplasia, a possible precursor lesion of adenocarcinoma of the lung.[42] Lau and colleagues demonstrated COX-2 overexpression in 19 of 20 lung cancer specimens using immunohistochemical analyses.[138] In another study, COX-2 overexpression was observed in both squamous cell carcinoma and adenocarcinomas of the lung.[40] Thus, COX-2 may provide a molecular target for therapy and prevention of lung cancer in smokers and nonsmokers. A pilot study of COX-2 inhibitors in high-risk tobacco smokers is ongoing at the Jonsson Cancer Center, University of California, Los Angeles. Other studies evaluating the role of celecoxib in heavy smokers are ongoing. In addition, celecoxib is being studied in neoadjuvant and therapeutic trials in combination with chemotherapy.

**Prostate Cancer**

Prostate carcinoma is the most commonly diagnosed cancer and the second-leading cause of cancer deaths in men in the United States. It is expected that approximately 189,000 new cases will be diagnosed and more than 30,200 deaths due to prostate cancer will occur in 2002.[85] Treatment for advanced prostate cancer often involves androgen ablation therapy and either surgical removal of the prostate, external beam radiation, or implantation of radioactive "seeds" into the prostate
(brachytherapy). Unfortunately, as prostate carcinoma progresses, it tends to become androgen independent and, therefore, refractory to hormone therapy.[142,143] Patients diagnosed in advanced stages of the disease have a poor prognosis.[144-146] Agents capable of inhibiting cell growth and sensitizing prostate carcinoma cells to stimuli that induce apoptosis, such as radiation therapy, would enhance the efficacy of treatment.

**COX-2: In Vitro and Preclinical Data**

Accumulating evidence suggests that overexpression of COX-2 is associated with resistance to apoptosis, thereby increasing the tumorigenic potential of a cancer.[123] Furthermore, selective inhibition of COX-2 has been demonstrated to induce apoptosis in prostate carcinoma cells in vitro.[76,147] These observations suggest that COX-2 inhibitors could be effective chemoprevention agents.

Lim and colleagues have examined the potential for COX inhibitors to be used to induce apoptosis in prostate cancer.[77] The COX-1 and -2 inhibitor sulindac was tested in vitro for proapoptotic activity in the prostate cancer cell lines PC3 and LNCaP, and in a normal prostate epithelial cell line PrEC. Apoptosis was quantified following treatment with either sulindac or sulindac sulfone (exisulind, Aptosyn). Forty-eight hours following treatment with either sulindac or exisulind, 50% of PC3 cells and 40% of LNCaP cells underwent apoptosis. However, PrEC cells showed no indication of apoptosis at similar concentrations of drug.[77]

Studies evaluating the effect of COX-2-specific inhibitors on angiogenesis in prostate carcinoma cell lines have been performed. Cell lines LNCaP and PC3, and the control cell line PrEC, were treated with two COX-2-specific inhibitors, etodolac (Lodine) and NS398.[78] Both compounds decreased cell proliferation in the carcinoma cell lines, but not in the normal prostate stromal cell line. A DNA fragmentation assay revealed that both compounds also induced apoptosis in the two carcinoma cell lines, but not in the normal stromal cell line.

**Clinical Data and Clinical Trials**

Using immunohistochemical analyses, Uotila and colleagues examined expression of COX-1 and -2 in prostate carcinoma tumors.[148] No significant difference in COX-1 expression was observed between normal prostate and prostate cancer tissue. However, their data revealed stronger staining of COX-2 in the prostate cancer cells compared with normal glandular epithelium of control prostates. Cyclooxygenase-2 expression was also elevated in the precursor lesion of prostate carcinoma, prostate intraepithelial neoplasia.[148]

Using similar techniques to quantify COX-2 expression, Kirschenbaum et al showed COX-2 overexpression in 86% of prostate intraepithelial neoplasia lesions and 87% of carcinomas collected during prostatectomy.[79,149] Furthermore, treatment of prostate carcinoma cells with a selective COX-2 inhibitor induced apoptosis in vivo and in vitro. The in vivo results revealed that the COX-2 inhibitor decreased microvessel density and angiogenesis. The investigators hypothesized that the decrease in angiogenesis was caused by inhibition of COX-2-induced expression of vascular endothelial growth factor.[79,149]

As a result of the preclinical experimental results showing activity for exisulind against prostate cancer, this phosphodiesterase/COX-1 and -2 inhibitor currently is being evaluated in a series of phase I/II clinical trials. These trials are examining prostate-specific antigen response and measurable disease response rate with exisulind as a single agent or in combination with docetaxel (Taxotere) ([Table 2]).[82-84] Secondary objectives include time to disease progression and duration of response in patients with prostate carcinoma.

Celecoxib is also undergoing clinical development for prevention/treatment of prostate cancer ([Table 2]).[82-84] In one phase I/II study, patients will be randomized to receive either celecoxib or placebo prior to radical prostatectomy.[82] The effect of celecoxib on COX-2 expression and angiogenic factors in the prostate will be examined.

These trials of COX-2 inhibitors will help determine their future role in treatment and...
chemoprevention of prostate cancer. Clearly, the mechanisms by which these drugs exert a proapoptotic effect in prostate carcinoma cells warrant further investigation.

**Breast Cancer**

The incidence of breast carcinoma varies with age and nationality. In the United States, the incidence increases rapidly to about age 45 years, then increases more slowly. At age 25 years, the incidence is approximately 5 cases in 100,000 women; at age 50 years, the incidence increases to 150 cases per 100,000 women. At age 75 years, the incidence rises to 200 per 100,000 women.[150,151] The development of breast cancer appears to be related to ovarian function and hormone production. However, a young age at first pregnancy, late menarche, and late menopause are factors with a protective effect against breast cancer.[152-154] Furthermore, oophorectomy before age 35 years reduces the risk of developing breast cancer by 70%. [155,156]

Therapy usually consists of a combination of surgery, radiation, and chemotherapy. Clearly, molecular target-specific chemoprevention agents with few or no adverse effects would be valuable to reduce morbidity and mortality rates from breast cancer.

**COX-2: In Vitro and Preclinical Background**

Prostaglandins have been implicated in breast carcinogenesis. Breast carcinoma cell lines[53,54] and rodent models[157] express elevated levels of COX-2 and prostaglandins compared with the normal tissues from which they arise. Inhibition of COX by NSAIDs reduces the development of chemically induced and transplantable mammary cancers.[55,158,159] It is also interesting that addition of hormones to human breast cancer cell lines[160] or rat mammary carcinoma cell lines[161] induces expression of prostaglandins.

Studies conducted by Rozic and colleagues examined the role of prostaglandins in the proliferation, survival, migratory, and invasive behavior, and angiogenic capacity in a highly invasive murine mammary tumor cell line.[55] Northern and Western blot analyses revealed a high expression level of COX-2 mRNA and protein, respectively. Their results indicated a high level of prostaglandin E₂ expression, which was completely abrogated by COX-2-specific inhibitors.

Migratory and invasive behavior was measured with an in vitro transwell migration/invasion assay. Cyclooxygenase-2-specific antagonists inhibited migration, while a COX-1-specific inhibitor had no effect on transwell migration. The COX-2-specific inhibitors also blocked angiogenesis in an in vivo assay. These studies suggest that COX-2-specific inhibitors may be effective for preventing breast tumor development and/or progression.[55]

Other studies also have shown that COX inhibitors block formation of breast tumors in mouse models.[55,162,163] Some studies suggest that COX-2 inhibitors may not only prevent mammary carcinogenesis, but may also prevent multidrug resistance in breast carcinoma.[164] The molecular mechanisms of prostaglandin-mediated progression of breast cancer are not characterized; however, one mechanism may involve the prostaglandin E₂ receptor. Fulton and colleagues demonstrated that advanced and metastatic breast carcinomas often express a mutation in the prostaglandin E₂ receptor. This mutation may also be involved in multidrug resistance.[165]

The potential of celecoxib to prevent mammary cancer was studied in the dimethylbenzanthracene (DMBA)-induced rat mammary tumor model by Harris and associates.[166] In this study, animals were fed a control diet or a diet supplemented with either ibuprofen (a COX-1 and -2 inhibitor) or celecoxib for 1 week prior to a single dose of DMBA. Both ibuprofen and celecoxib groups showed a statistically significant reduction in tumor incidence. However, the reduction in tumor incidence observed in the celecoxib group was greater than that observed in the ibuprofen-treated group. Furthermore, Alshafie and colleagues demonstrated that celecoxib also had a therapeutic effect in the DMBA-induced rat mammary model.[167]

**Clinical Data and Clinical Trials**
Hwang and colleagues demonstrated that COX-2 is overexpressed in breast hyperplasia and atypical hyperplasias.[56] Similarly, these investigators showed that COX-2 is overexpressed in > 56% of breast cancers. Interestingly, COX-2 overexpression was more apparent in ductal carcinomas in situ than in metastatic breast cancers, suggesting that COX-2 may play an important role in the early carcinogenesis of the breast.[40] The COX-2-specific inhibitors may be ideal candidates for chemoprevention of breast cancer for several reasons. The toxicity profile appears to be acceptable for premenopausal women because COX-2 inhibitors do not cause perimenopausal symptoms. However, long-term effects of the use of celecoxib in these subjects is being evaluated in clinical studies. They may be effective in both estrogen-receptor-positive and estrogen-receptor-negative disease.

Several clinical trials with celecoxib are at different points of development. One such trial has been initiated examining efficacy of celecoxib and trastuzumab (Herceptin) in women with HER2/neu-overexpressing metastatic breast cancer that is refractory to trastuzumab (Table 2).[82-84] Multiple trials are ongoing to evaluate the effect of celecoxib in precancerous, in situ, and invasive breast carcinoma.

**Gastric Cancer**

The incidence of gastric cancer varies remarkably in different parts of the world. The incidence is relatively high in Japan and Chile, with approximately 58.4 cases per 100,000 men and 29.9 cases per 100,000 women.[168] The incidence of gastric cancer is lowest in the Dominican Republic and Thailand, where the rate is approximately 5% of that reported in Japan.[168,169] The high rate of gastric carcinoma in Japan is thought to be caused in part by the high consumption of cured meat and fish. These products contain a high concentration of N-nitroso compounds that cause formation of potentially carcinogenic endogenous nitrosamines.[170,171] In the United States, 21,600 cases of gastric cancer are expected in 2002.[85] However, the incidence in the United States and Japan has dropped in recent years, perhaps due to an increased awareness of proper dietary habits.[172,173]

**COX-2: Clinical Data**

Some studies suggest that a *Helicobacter pylori* infection predisposes a patient to gastric cancer, perhaps owing to increased expression of COX-2.[174-176] Leung and colleagues examined the association between expression of COX-2 and the presence of a missense mutation in the tumor suppressor gene p53.[177] Wild-type p53 normally binds to cis elements within the promoter region of the COX-2 gene and inhibits its transcription. Of 39 patients with gastric cancer, 19 (49%) overexpressed COX-2.[66] Of these, the patients with the strongest COX-2 expression also had a mutated p53 gene.

In addition, the cancer in these patients with higher COX-2 expression and mutated p53 gene was more aggressive, with more lymphatic invasion and metastases. These data suggest that mutation of the p53 gene may have a direct effect on expression of COX-2 in gastric carcinoma, and that increased COX-2 expression may be associated with poor prognosis.[66,177]

Other studies revealed a direct relationship between expression of COX-2 mRNA and increased tumor invasion. Thus, COX-2 inhibitors may provide effective prevention in patients with *H pylori* infection and in patients with this risk factor for gastric cancer. Clinical trials should be developed to test these agents in this patient population.

**Bladder Cancer**

Bladder cancer is the fourth leading cause of cancer in men and the eighth in women. Furthermore, it is the ninth and fourteenth leading cause of US cancer deaths in men and women, respectively.[178] Many etiologic factors have been identified including occupation (eg, close contact with chemical carcinogens),[179,180] diet,[181,182] chronic bladder infections,[183,184] and smoking.[185,186]

The vast majority of bladder cancers arise from bladder papilloma precursors, providing significant
opportunities for the development of chemoprevention strategies.

**COX-2: In Vitro and Preclinical Background**

Recent animal studies indicate that nonspecific COX inhibitors and specific COX-2 inhibitors reduce the incidence of bladder carcinoma induced by chemical carcinogens.[187,188] Khan and colleagues examined COX-1 and -2 expression in normal dogs and in dogs with transitional cell carcinoma.[49] There was no difference in COX-1 expression between normal and malignant bladder tissue; however, COX-2 was only expressed in carcinoma and in new blood vessels in the tumor tissue.

Using two rodent models of bladder cancer, Grubbs and colleagues demonstrated that the COX-2-specific inhibitor celecoxib was effective in inhibiting chemically induced bladder cancer.[189] Male mice treated with N-butyl-N-(4-hydroxy-butyl)nitrosamine (OH-BBN) compared with no treatment developed transitional and squamous cell urinary bladder cancer with high morbidity. Mice pretreated with celecoxib 7 days before initiation of 12 weekly doses of OH-BBN had a 75% decrease in the incidence of bladder cancer. There was no decrease in development of preneoplastic lesions, suggesting that COX-2 may play a role during the progression stages of bladder carcinoma.

Similar results were observed in a rat model using the same chemical initiator and time course.[189] These data suggest that COX-2-specific inhibitors may not prevent initiation of carcinogenesis in the urinary bladder. However, they may be effective in preventing bladder carcinoma in individuals identified as high risk and for treatment of early-stage bladder cancer.

**Clinical Data and Clinical Trials**

In humans, several studies have shown that COX-2 is expressed in invasive transitional cell carcinoma, but not in normal bladder tissue. Expression of COX-2 is localized to the carcinoma cells, whereas there appears to be no COX-2 expression in the stroma.[50-52] It is also interesting that in studies examining the molecular characteristics of bladder carcinoma in patients in close proximity to Chernobyl following the nuclear accident in 1986, Romanenko and colleagues showed that overexpression of COX-2 was associated with mutations in the p53 gene.[190] These findings are similar to data indicating a relationship between mutant p53 and COX-2 expression in gastric cancer.[177]

Currently, a large clinical study examining inhibition of COX-2 and recurrence of bladder cancer is ongoing at The University of Texas M. D. Anderson Cancer Center, Houston (Table 2).[82-84] This study is designed to compare the time to recurrence following treatment with celecoxib or placebo in patients with superficial transitional cell carcinoma of the bladder at high risk for recurrence. This study will also correlate the modulation of one or more biomarkers with recurrence of bladder cancer and evaluate the quality of life of patients enrolled on each of the two regimens.

**Esophageal Cancer**

During the last decade, the incidence of esophageal adenocarcinoma has increased at a disproportionately rapid rate.[191] The majority of esophageal cancers arise in patients with the premalignant condition Barrett’s esophagus, which manifests by the replacement of normal esophageal epithelium with a columnar type.[192-195] Barrett’s esophagus is frequently associated with high-grade dysplasia and aneuploidy in esophageal epithelium.[196-199] The condition develops from chronic, severe gastroesophageal reflux. Patients afflicted with Barrett’s esophagus have a 30- to 40-fold increased risk for development of esophageal adenocarcinoma.[200,201] Postoperative morbidity is high for esophageal cancer, and survival is not favorable (13% to 30% at 5 years).[202-205] Clearly, chemoprevention strategies are needed.

**COX-2: In Vitro and Preclinical Background**

Research conducted by Li and colleagues demonstrated that aspirin retarded cell growth in an esophageal adenocarcinoma cell line.[206] Growth inhibition was shown to be dose and time dependent.[63] Subsequently, they tested the effect of the COX-2-specific inhibitor NS398 on
apoptosis and expression of genes that regulate apoptosis. In vitro, the COX-2-specific inhibitor induced apoptosis in several esophageal adenocarcinoma cell lines through a cytochrome C-dependent pathway. There was a direct relationship between apoptosis and the level of COX-2 expression. Caspase-9 and caspase-3 were activated by NS398, and addition of a caspase inhibitor reversed the apoptotic effect of the COX-2 inhibitor.[206] These data suggest that COX-2 specific inhibitors may be promising for chemoprevention and treatment of esophageal adenocarcinoma.

Clinical Data

Kandil and colleagues examined esophageal pinch biopsy specimens from patients with Barrett’s esophagus from normal and abnormal tissue.[207] Western analyses for COX-2 protein showed an increase in COX-2 expression in 41% of the Barrett’s esophagus tissue biopsies. No COX-2 expression was observed in adjacent normal tissue. It is of interest that COX-2 was found in Barrett’s esophagus tissue with or without dysplasia, suggesting that COX-2 may play a role in the early stages of development of adenocarcinoma.[45] Additionally, COX-2 is overexpressed in adenocarcinoma arising from Barrett’s esophagus at all stages.[46,208,209]

Currently, a clinical study is ongoing coordinated by the Johns Hopkins Comprehensive Cancer Center, Baltimore, to evaluate the efficacy and safety of celecoxib in patients with Barrett’s esophagus (Table)

Pancreatic Cancer

Pancreatic cancer is a highly invasive, aggressive disease and is the fifth leading cause of cancer deaths in the United States.[210] Although the DNA synthesis inhibitor gemcitabine (Gemzar) can have a modest effect on survival, the majority of patients succumb to their disease within 6 months following diagnosis.[211,212]

COX-2: In Vitro and Preclinical Data

Studies were conducted to measure the effects of COX-nonspecific and COX-2-specific inhibitors on cell growth and apoptosis in four pancreatic cancer cell lines expressing COX-2.[213] Cell growth, measured by [³H]-thymidine incorporation, showed a dose-dependent decrease in cell proliferation with both the nonspecific COX inhibitors and the COX-2-specific inhibitor NS298.

Yip-Schneider and colleagues examined the effects of COX inhibitors in combination with gemcitabine in vitro.[74,214] The COX-nonspecific and COX-2-specific inhibitors caused cell cycle arrest primarily in the G1/G0 phase through decreased expression of cyclins, whereas gemcitabine caused arrest in the S phase due to its incorporation into DNA. It is of great interest that COX inhibitors in combination with gemcitabine had an additive effect on inhibition of cell growth. No significant effect on apoptosis was observed in any of the test groups, suggesting that the drugs alone and in combination may induce cell senescence.[74,214]

Clinical Data

Tucker and colleagues examined expression of COX-2 mRNA in tissue isolated from pancreatic cancer patients using quantitative reverse transcriptase polymerase chain reaction.[75] These studies revealed a 60-fold increase in expression of COX-2 mRNA in tissue isolated from 9 of 10 pancreatic adenocarcinomas compared with adjacent normal pancreatic tissue. Immunohistochemical staining indicated that COX-2 expression was localized to the malignant epithelium. It was also demonstrated that COX-2 was expressed in human pancreatic carcinoma cell lines.[75]

Clearly, the effectiveness of COX inhibitors in combination with gemcitabine may have potential for treatment of pancreatic cancer, but continued clinical development is required. Several studies evaluating the effect of celecoxib in combination with chemotherapy for pancreatic cancer have been initiated, including a phase II clinical trial of celecoxib and gemcitabine at the Arizona Cancer Center.
Conclusions

Cyclooxygenase-2 is known to be a mediator of inflammation and other immune processes. It is therefore of interest that several of the malignancies in which COX-2 is overexpressed are associated with a chronic inflammatory condition. For example, esophageal carcinoma is associated with Barrett's esophagus, and nonmelanoma skin cancers are associated with UV damage. In addition, gastric carcinoma is associated with an ulcerative condition caused by infection with H pylori. The data suggest that inhibition of COX-2 may inhibit carcinogenesis at a very early stage and may completely block tumor formation in tumors that arise from nonmalignant inflammatory precursors. As discussed in this review, preclinical and clinical data support the hypothesis that COX-2 plays a role in oncogenesis, and that COX-2 inhibitors may offer effective chemoprevention strategies (summarized in Figure 4).

Epidemiologic studies revealing an inverse correlation between the incidence of colon cancer and regular use of NSAIDs provided initial clues suggesting that COX inhibition may be an effective intervention approach to preventing cancer.[215-217] Because NSAIDs are known to block prostaglandin synthesis by inhibition of the COX enzymes, it was hypothesized that aberrant prostaglandin synthesis may contribute to colorectal neoplasia. Further investigations documented that COX-2 is barely detectable in normal colon mucosa, but is significantly upregulated in colon carcinoma.[34,47] Cyclooxygenase-2 also is overexpressed in intestinal adenomas in rodent models of intestinal tumorigenesis and in a high percentage of colorectal adenomas.[218,219]

More recently, in familial adenomatous polyposis patients, the COX-2-specific inhibitor celecoxib caused a 28% reduction in colorectal adenomas after 6 months of treatment at a dose of 400 mg twice-daily, whereas controls given placebo experienced no significant reductions in adenoma numbers.[102] This finding has established celecoxib as a potentially valuable chemoprevention agent in patients at high risk of sporadic colorectal adenoma recurrence.[48,220-222]

Currently, there are three phase III trials under way to test different doses of celecoxib in the prevention of sporadic colorectal polyp recurrence. Clearly, further examination of COX-2 inhibitors in prevention and treatment of cancer is warranted. Because of the favorable safety profile in healthy individuals, COX-2 inhibitors may provide an effective and safe option for cancer chemoprevention.

References:


98. Labayle D, Fischer D, Vielh P, et al: Sulindac causes regression of rectal polyps in familial...


135. Bouchard L, Castonguay A: Inhibitory effects of nonsteroidal anti-inflammatory drugs (NSAIDs)


208. Lord RV, Danenberg KD, Danenberg PV: Cyclooxygenase-2 in Barrett’s esophagus, Barrett’s adenocarcinomas, and esophageal SCC: Ready for clinical trials. Am J Gastroenterol 94:2313-2315,
1999.


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