Celecoxib With Chemotherapy in Colorectal Cancer

Cyclooxygenase-2 (COX-2) is the enzyme that normally synthesizes prostaglandins during an inflammatory response.

Colorectal cancer is a significant cause of morbidity and mortality for men and women in the United States. Overall, almost 6% of Americans will develop this disease during their lifetime. Estimates for 2001 called for 138,900 incident cases and 57,100 deaths from colorectal cancer, making it the second most common visceral malignancy and the third most common cancer killer in both genders.[1] Twenty percent of patients present with metastatic disease,[2] and approximately 30% of patients ostensibly cured by surgical resection will develop unresectable locally recurrent or distant disease. The 5-year survival rate for patients with metastatic disease is only 6%.[2] suggesting a need for more effective chemotherapy for advanced tumors.

Routine chemotherapy for metastatic colorectal cancer has been unsatisfactory, although fluorouracil (5-FU)-based chemotherapy has been used for 5 decades. The current standard therapy for patients with untreated colorectal cancer is the 5-FU plus leucovorin combination given with irinotecan (CPT-11, Camptosar), a topoisomerase I inhibitor.[3] "Standard" North American dosing (each drug given weekly × 4 every 6 weeks) achieves response rates of 39% and a median overall survival of 14.8 months, with grade 3/4 diarrhea occurring in 23% and severe to life-threatening neutropenia occurring in 54% of patients. Administering at least some portions of the 5-FU by continuous infusion decreases toxicity and may be associated with longer median survival.[4] Overall, most patients with metastatic colorectal cancer die within 2 years; there is clearly significant room for improvement in outcome.

Arachidonic Acid and Eicosanoids: Roles in Carcinogenesis and Potential Chemoprevention

Chemopreventive agents play a role in impeding the development of colorectal cancer, and some of these drugs might be useful in treating established disease as well. The arachidonic acid cascade contains enzymes linked to colorectal cancer development, and existing chemopreventive agents impair those reactions. Arachidonic acid, which is derived from the diet, resides in cell membranes in ester form with phospholipids. High saturated fat diets promote colorectal cancers initiated by chemical carcinogens,[5] and while the mechanism is not entirely understood, tumor promotion also may be related to a change in the composition of the colorectal cancer cell membranes.

Nicholson et al analyzed the fatty acid content of normal colonic mucosa and tumor mucosa from Wistar rats.[6] Weanling rats were fed a low- or high saturated fat diet, and a subsample of rats in each group received the carcinogen azoxymethane intraperitoneally. After humane killing, colon and rectum were excised, and fatty acid methyl esters in the cell membranes were analyzed. There was a significantly higher proportion of arachidonic acid in tumor cell membranes as compared with normal colorectal tissues, regardless of dietary composition. The higher saturated fat diet was associated with greater tumor promotion than was the low-fat diet.

Eicosanoids are 20-carbon arachidonic acid metabolites that take the form of prostaglandins, thromboxanes, and leukotrienes. Series-2 prostaglandins are specific substances hypothesized to have a role in colorectal carcinogenesis, since they modulate the growth of several cell types. Indirect evidence to support this exists: arachidonic acid mobilization is linked to a wide variety of biologic signal transduction pathways,[7] and this process is fairly tightly regulated in the gastrointestinal (GI) tract. Prostanoid synthesis is enhanced by a variety of growth factors, and PGH2 synthase (another name for cyclooxygenase [COX]) is homologous to the product of a proliferation-associated gene.[8] Human colonic mucosa is known to have the ability to synthesize multiple eicosanoids, and tumor cells produce larger quantities of certain prostaglandins than does surrounding mucosa.
Other non-growth-regulated mechanisms for prostaglandin-induced tumor initiation and promotion exist. For example, tumor growth is enhanced in the setting of immunosuppression. Colony-stimulating factors released by tumors can cause mononuclear cells to secrete PGE₂, which influences activity of T cells and natural killer cells, the cells that may be involved in immune surveillance.[9] Prostaglandins regulate platelet function, and tumor-platelet aggregates are proposed to activate cancer cells for vascular attachment, promoting metastases.[10] PGI₂, a platelet inhibitor, inhibits metastases of colon carcinoma. Also, E-series prostaglandins are angiogenic, and tumor-induced angiogenesis is strongly tied to growth and metastasis.[11]

**Cyclooxygenase-2 (COX-2) Expression and Inhibition**

At least two COX enzymes are present in humans: COX-1 and COX-2.[12] COX-1 is a constitutive enzyme involved in homeostasis of tissues such as gastric and renal epithelium. COX-2 is an enzyme induced by a variety of mitogens, cytokines, and growth factors; it is associated with PG production at sites of inflammation. Eberhart et al demonstrated that COX-2 gene expression (mRNA) was found in low-to-undetectable levels in normal colorectal mucosa, but was increased in the majority of adenocarcinomas studied.[13] Interestingly, up-regulation of COX-2 also was demonstrated in a subset of adenomas, the precursors of adenocarcinomas. COX-2 expression has been demonstrated in tumors from a variety of GI sites, including squamous cell carcinoma and adenocarcinoma of the esophagus, gastric cancer, pancreatic cancer, and well-differentiated hepatocellular carcinoma. It also has been seen in non-GI cancers, such as squamous cell tumors of the head and neck, transitional cell carcinoma of the bladder, non-small-cell lung cancer, cervical cancer, retinoblastoma, prostate cancer, and glioma.

More importantly, COX-2 overexpression is likely related to the acquisition and maintenance of an invasive metastatic phenotype. Tsujii and DuBois showed that COX-2 overexpression in rat intestinal epithelial (RIE) cells led to phenotypic changes that could enhance their tumorigenic potential.[14] These cells appeared resistant to apoptosis, or programmed cell death, although the resistance could be overcome by adding sulindac (Clinoril), a nonspecific COX inhibitor. Tsujii also transfected human colon cancer cells (Caco-2) with a COX-2 expression vector and selected cells that constitutively express the COX-2 gene.[15] Those cells demonstrated potent extracellular matrix degrading abilities, leading to their becoming sixfold more invasive than control cells. Again, sulindac almost completely inhibited this new property.

Shao and associates described the expression of COX-2 in azoxymethane-induced rat primary colonic tumors and human metastatic colon carcinomas.[16] Seventy-five percent of metastatic tumors displayed COX-2 immunoreactivity, while COX-1 activity was demonstrated in interstitial, but not tumor, cells. Recently, Tomozawa and associates showed that expression of COX-2 in patients who had been potentially curatively resected of large bowel malignancy correlated with risk of tumor recurrence.[17] "High" expression of COX-2 (21% of cases) was the only independent factor significantly related to disease-free survival.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX enzymes and subsequently reduce eicosanoid production. Pollard et al demonstrated that Sprague-Dawley rats, which develop intestinal cancers in response to intraperitoneal injection of a dimethylnitrosamine derivative, had significantly smaller tumors if they were given drinking water containing the nonspecific COX inhibitor, nonsteroidal anti-inflammatory drug indomethacin (Indocin).[18] In rats receiving other nonspecific NSAIDs, such as sulindac, both the number of tumors per mouse and the number of mice with tumors decreased after treatment with the carcinogen 1,2-dimethylhydrazine.[19] Sulindac also slowed growth of tumors present in rats.[20]

Specific COX-2 inhibitors have similarly been tested preclinically. Oshima and associates used a selective inhibitor on ApcΔdelta716 knockout mice, a model for familial adenomatous polyposis.[21] A second knockout, that of the COX-2 gene, markedly decreased the size and number of intestinal polyps in offspring. Use of a selective COX-2 inhibitor also significantly decreased polyp development. Sheng and associates demonstrated that treatment of transformed rat intestinal epithelial cells with a selective COX-2 antagonist both inhibited growth and induced apoptosis.[22]

**Clinical Evidence of NSAID Efficacy in Colorectal Cancer**

Evidence shows that NSAIDs can abolish established polyps and possibly prevent progression to cancer in humans. Frequently, colorectal adenomas are precursors to bowel neoplasms, and patients with familial adenomatous polyposis (FAP) inevitably develop cancer unless the colon is removed. Gardner's syndrome consists of an autosomal dominant variation of FAP, with afflicted patients also manifesting extra-GI soft tissue growths. Waddell and colleagues reported the effect of sulindac on...
colonic polyposis and neoplasms in 11 patients with Gardner’s syndrome or familial polyposis.[23] Seven patients had subtotal colectomy with ileorectal anastomosis, and four had intact colons. All were given sulindac at typical doses, and all but one were observed for 1 to 16 years using frequent endoscopy or barium enema. Nearly all remaining polyps in these groups disappeared over 6 to 12 months, and no colorectal carcinomas developed in any patient. Upon drug discontinuation, two of three patients had regrowth of polyps.

Rigau and colleagues assessed sulindac treatment in seven patients with FAP, Gardner’s syndrome, nonfamilial polyposis, and multiple hyperplastic polyposis.[24] All had diffuse colonic polyps. A “marked reduction” in the number and size of polyps was seen during the first 6 months of therapy, and discontinuation of sulindac was associated with recurrence in three of four patients. After resuming sulindac treatment, these three again had regression in the number and size of polyps. In this study, PG generation (PGE\(_2\) and 6-keto-PGF\(_{1\alpha}\)) in the colonic mucosa was significantly reduced after 6 months of therapy in all patients assessed. This trial was significant, because the patients did not undergo surgery, which itself has been reported to affect polyp growth.

Recently, Steinbach and associates demonstrated that FAP patients given the COX-2 inhibitor celecoxib (Celebrex) at a dosage of 400 mg orally twice daily for 6 months had a significantly reduced number of colorectal polyps and overall polyp burden vs those given placebo or a lower celecoxib dose.[25]

Data from several mature epidemiologic studies support a role for NSAIDs in the prevention of human colorectal cancer. In a large hospital-based case-control study, Rosenberg and associates found that regular and sustained NSAID use reduced colorectal cancer incidence by 50%. [26] Thun and colleagues tested the chemoprevention hypothesis in a large prospective mortality study and showed a 40% lower death rate from colon cancer in patients using aspirin regularly.[27]

**Celecoxib: A Selective COX-2 Inhibitor**

Highly selective COX-2 inhibitors exist and are uniquely suited to chemotherapeutic and chemoprevention trials for colorectal cancer. The COX-2 inhibitor celecoxib is 300 times more active against COX-2 than it is against COX-1. Unlike aspirin, which covalently binds to COX, celecoxib inhibits without permanently modifying the enzyme. Its anti-inflammatory activity compares favorably with that of indomethacin in the carrageenan footpad edema model (ED\(_{50}\) = 50 mg/kg) in terms of decreased PG production.[28] Furthermore, selective COX-2 inhibitors appear to be safer than are nonspecific NSAI\(\text{Ds. Celecoxib has no effect on platelet aggregation or bleeding time, demonstrating a lack of inhibition of COX-1. Mild to moderate side effects include dyspepsia, diarrhea, and abdominal pain, none of which occurs in more than 10% of patients. Patients who are free of cancer have been treated with celecoxib doses ranging from 100 to 400 mg given twice daily. Celecoxib has been associated with a significantly lower incidence of endoscopically documented and/or symptomatic GI ulcers as compared with that associated with naproxen or ibuprofen.[29,30] As with nonspecific COX inhibitors, there is a strong preclinical rationale for the use of celecoxib in treatment of colorectal cancer. COX-2-derived prostaglandins induce tumor neoangiogenesis, which promotes tumor growth. Celecoxib potently suppresses this prostaglandin formation and, thus, is antiangiogenic.[31] When given to nude mice implanted with human HT-29 colon cancer cells, celecoxib inhibited both primary tumor growth and lung metastases (personal communication, J. Masferrer, MD, 2000).

The U.S. Food and Drug Administration has approved celecoxib for single-agent treatment of patients with arthritis and with FAP, and it is reasonable to test this agent in treatment of human malignancy. Nonselective COX inhibitors have been safely combined with chemotherapy. A phase I trial assessed the feasibility of combining 5-FU/levamisole (Ergamisol) with sulindac.[32] Fifteen patients with advanced colorectal cancer were given 5-FU/levamisole as employed in the Intergroup study (450 mg/m\(^2\) of 5-FU given via IV push on days 1 to 5, then once weekly beginning on day 29; and 50 mg of levamisole orally three times daily on days 1 to 3 of the first cycle, then repeated for 3 days on alternate weeks beginning on day 15) plus 150 mg of sulindac twice daily beginning on the first day of treatment. The principal toxicity was myelosuppression; four of 15 patients experienced grade 3/4 neutropenia, two had grade 3 anemia, and none experienced severe or life-threatening thrombocytopenia. No chemotherapy-related deaths were reported. The opinion was that the addition of sulindac to standard adjuvant treatment did not increase short-term toxicity. An ongoing phase I trial testing escalating doses of celecoxib in combination with the standard 5-FU and leucovorin regimen of the North Central Cancer Treatment Group (NCCTG) has not demonstrated an increase in toxicity over that expected from use of chemotherapy alone (unpublished data, Oregon Health Sciences University, 2001).

Ongoing trials are testing the role of COX-2 inhibitors not as chemopreventive agents, but as a
treatment of established cancer. The Hoosier Oncology Group is combining celecoxib (400 mg given orally every 12 hours) with irinotecan, 5-FU, and leucovorin in the treatment of metastatic large bowel cancer. Glutamine, a conditionally essential amino acid often depleted in advanced colorectal cancer patients, is added for its potential role in preventing or diminishing chemotherapy-associated GI toxicities. This is a particularly attractive regimen given the possibility that the COX-2 inhibitor might block prostaglandin and thromboxane production induced by the chemotherapy, thus also leading to less diarrhea. Planned accrual is 22 patients; early findings show sufficient evidence of activity continuing past the first early stopping rule (personal communication, C. Sweeney, MBBS, 2001).

Another ongoing study is an Oregon Health Sciences University-based, multi-institutional trial of chemotherapy plus celecoxib (400 mg orally given twice daily), again in patients with untreated metastatic colorectal cancer. Early results have demonstrated some evidence of efficacy in terms of objective response rates; the results also suggested that toxicity, particularly neutropenia and diarrhea, might be less than that expected with the chemotherapy regimen alone. A trial that has been proposed to replace the current Intergroup colorectal cancer metastatic disease trial would assess standard American dosing of irinotecan/5-FU/leucovorin vs an infusional regimen (modified FOLFIRI, another regimen containing irinotecan, 5-FU, and leucovorin), plus or minus 400 mg of celecoxib bid. That trial has associated translational endpoints: investigators will examine polymorphism of genes involved in metabolic pathways of fluoropyrimidines (TS, DPD, TP, and others) and irinotecan (UGT1A1, XRCC-1, and others) to find out if they can be used to predict toxicity and clinical outcome. In addition, expression of other genes involving downstream of COX-2 inhibition (E-cadherin, integrins, vascular endothelial growth factor, and interleukin-8) will be correlated with the chemotherapeutic efficacy.

Conclusions

In conclusion, COX-2 inhibitors have a proven role in prevention of neoplastic disease, and a strong laboratory-based rationale supports their use in combination with chemotherapy in the treatment of established tumors, particularly colorectal cancer. Further research will help to define their value in colorectal cancer.

References:


Source URL:
http://www.diagnosticimaging.com/review-article/celecoxib-chemotherapy-colorectal-cancer

Links:
[1] http://www.diagnosticimaging.com/review-article