COX-2 Inhibition in Clinical Cancer Prevention

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Colorectal cancer is an excellent model for studying cancer prevention by means of secondary (eg, polypectomy to remove a precursor adenoma) and primary

Introduction

In patients who develop adenocarcinomas, there is typically a progression from normal epithelium, through some inflammatory, metaplastic, or other intermediate stage, to dysplasia and invasive cancer. The progression is by no means invariable and indeed may be reversible. Colorectal cancer exemplifies this progression and serves as an excellent model for investigating opportunities in cancer prevention by means of various secondary (eg, polypectomy to remove the precursor adenoma) and primary (chemoprevention) strategies.

We and many others have begun to explore opportunities in colon cancer chemoprevention through clinical trials involving groups at increased risk of colorectal cancer: patients with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, and sporadic adenoma. This article briefly reviews data from our large trial of a selective COX-2 inhibitor, describes the designs for our current hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis trials (as well as ongoing sporadic adenoma trials), and includes comments on trials with other agents.

Familial Adenomatous Polyposis

Patients with familial adenomatous polyposis have a germline mutation in the adenomatous polyposis coli (APC) gene.[1] The consequence of this is the development of hundreds of adenomas, typically during adolescence. If untreated, as by prophylactic colectomy or proctocolectomy, the risk of colorectal cancer is nearly 100%. Following colectomy, subjects remain at risk of duodenal carcinoma and, if proctectomy is not performed, of rectal cancer; these areas have hence been targeted in surveillance and chemoprevention interventions.

Historically, cancer prophylaxis has consisted of colectomy followed by proctosigmoidoscopic surveillance and ablation of recurrent rectal polyps, or more recently and aggressively, prophylactic proctocolectomy with restorative ileal pouch reservoir/anal anastomosis. Management of risk of duodenal neoplasia has been particularly vexing because of the variable natural history of duodenal adenomas; the lack of effective, safe endoscopic measures to ablate the flat, spreading lesions; and the morbidity associated with aggressive surgical intervention—typically pancreaticoduodenectomy.

Though prophylactic surgical interventions are well accepted in familial adenomatous polyposis, the possibility of medical approaches has been explored. The nonsteroidal anti-inflammatory drug (NSAID) sulindac has been reported to cause complete or near-complete regression of rectal adenomas, initially in uncontrolled trials[2-4] and later in placebo-controlled investigations.[5] More modest regression of rectal adenomas has been reported in two larger placebo-controlled studies.[6,7] No cases of complete regression were observed, and adenomas recurred within several months of cessation of the sulindac.[5,6] No long-term efficacy studies of sulindac have been carried out, and there are case reports of cancers occurring while taking sulindac.[8]

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer has until recently been a clinical diagnosis involving the familial pattern of early-onset and/or multiple primary colorectal cancer, with or without the presence of certain extracolonic tumors. In many families colon tumors cluster in the right colon.
Adenomas may be completely absent and rarely number more than a few. The mode of inheritance for hereditary nonpolyposis colorectal cancer is autosomal dominant, with penetrance for colorectal cancer estimated at about 80% by age 70. The mean age at cancer onset is approximately 45 years but ranges from 20 to 80+ years, thus overlapping with the age distribution of sporadics.

Stomach and small bowel adenocarcinomas occur in excess, but are sufficiently infrequent that surveillance is not usually recommended. In addition to colorectal and other gastrointestinal tumors, hereditary nonpolyposis colorectal cancer includes a number of extraintestinal tumors. Lacking any pathognomonic features, the significance of any given tumor in a particular patient is problematic. Tumors most commonly involve the endometrium, followed by the ovary and the uroepithelium (ureter and renal pelvis). Peculiar skin tumors (sebaceous adenoma, carcinoma, and keratoacanthoma) occur in a subset of families with the so-called Muir-Torre syndrome.

**Management**

As in familial adenomatous polyposis, the management of hereditary nonpolyposis colorectal cancer involves recognition of risk, followed by appropriate surveillance and surgical intervention. All must be enhanced, compared to the average-risk patient. In a sufficiently striking family, colorectal cancer risk to offspring of affected parents approaches 50%. Molecular genetic testing will detect mutations in one of the "hereditary nonpolyposis colorectal cancer genes" in up to 85% of families.

Assuming such a mutation is identified, offspring of affected parents can be segregated into two groups: those at population risk (noncarriers) and those whose risk approaches 100% (carriers). In carriers, colonoscopy is recommended, beginning at age 20 to 30 and repeated at intervals of 1 to 5 years (the broad range reflects a lack of hard data and a lack of consensus among experts). Noncarriers will require no further enhanced evaluation, assuming accuracy of the genetic testing.

When adenocarcinomas are detected, subtotal colectomy with ileorectal anastomosis is urged. Residual risk to the rectum exists postcolectomy, but its magnitude is uncertain and probably not great enough to warrant proctectomy. The approach to the patient with an adenoma is uncertain. Most would perform simple endoscopic polypectomy, but the possibility of prophylactic colectomy may be increasingly considered in known mutation carriers, particularly when difficult-to-remove right-sided sessile lesions are involved. Surveillance for extracolonic tumors has received little attention.

**Molecular Advances**

The chronology of molecular advances in hereditary nonpolyposis colorectal cancer is interesting. Unlike familial adenomatous polyposis, there was no good clue as to the possible location of a susceptibility locus, though several "candidate" loci, such as the APC, p53, and DCC (deleted in colorectal carcinoma) genes, were evaluated and excluded. Rather, establishing genetic linkage in hereditary nonpolyposis colorectal cancer required a search through the human genome, facilitated by the developing library of known, linked genetic polymorphisms.

In 1993 such linkage was established to a locus on chromosome 2 and quickly confirmed. Within a year, the gene had been cloned and found to show homology in nucleotide sequence to a member of a yeast DNA "mismatch repair" gene (MutS). Because linkage studies at this locus had failed to account for a majority of families that appeared to have hereditary nonpolyposis colorectal cancer, additional loci were evaluated and a second gene identified. When cloned, this gene was also found to show homology to a member of the yeast mismatch repair family of genes.

It was then concluded that perhaps other human genes from this mismatch repair family might also account for cases of hereditary nonpolyposis colorectal cancer. The library of human DNA sequences was searched to determine if there were other areas that showed significant homology to the other representatives of the mismatch repair genes of lower species. Several additional human mismatch repair genes were identified and found to account for a small proportion of hereditary nonpolyposis colorectal cancer families.

As in the case of familial adenomatous polyposis, each of these discoveries carried potential
implications for management. Establishment of linkage enabled recognition of carriers of susceptibility through performance of linkage analysis utilizing polymorphic flanking markers. Cloning of the genes enabled direct testing of individual affected members of hereditary nonpolyposis colorectal cancer families, without having to resort to linkage analysis.

Chemoprevention

With recognition of hereditary nonpolyposis colorectal cancer as a distinct entity with predictable colorectal cancer risk, efforts in chemoprevention began. Cats and colleagues[9] administered oral calcium to a small series of subjects at risk of hereditary nonpolyposis colorectal cancer tumors. The trial end point was epithelial proliferation or labeling index, as measured by bromodeoxyuridine incorporation. No significant difference in posttreatment labeling index was observed between the study group receiving 1.5 g of CaCO3 and the placebo group. The design of our ongoing study, utilizing celecoxib (Cerebrex), a selective COX-2 inhibitor, is outlined below.

Another multicenter trial centered in Europe[10,11] but intercontinental in scope uses aspirin and resistant (high-amylose, fermentable) starch (Novelose) in a factorial design. Its accrual goals are very ambitious: approximately 1,200 subjects from 55 institutions, and accrual is underway at this time. It is intended to have sufficient power to identify a treatment effect, namely reduction in adenoma incidence in hereditary nonpolyposis colorectal cancer subjects, during a follow-up period of at least 2 years for each enrolled subject. Eligibility criteria are similar to those used in our hereditary nonpolyposis colorectal cancer celecoxib trial outlined in this article.

Sporadic Adenoma/Carcinoma

Nonfamilial, sporadic, or common adenomas and carcinomas are a much more common problem than either familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer. However, the risk of incident neoplasia in any given subject, even one with a previous neoplasm, is comparatively low. Consequently, evaluation of impact of intervention requires a much larger sample size. Thus, in the National Polyp Study evaluation of the impact of adenoma follow-up by means of colonoscopy, more than 1,400 subjects were required to demonstrate a significant surveillance benefit. Many epidemiologic studies have shown benefits of NSAIDs, notably aspirin, in reducing risk of sporadic colorectal neoplasia.[12-15]

Use of COX-2 Inhibitors in Colorectal Neoplasia Chemoprevention

NSAIDs have been shown in several experiments to decrease carcinogen-induced bowel tumors in rodents.[16,17] In humans, epidemiologic studies have shown a salutary effect of NSAIDs in reducing rates of sporadic colorectal adenoma, cancer, and mortality attributed to colorectal cancer.[12-15] Sulindac, a common NSAID, has, in preliminary investigations[2,3] and randomized placebo-controlled trials,[5-7] induced regression of colorectal adenomas in subjects with familial adenomatous polyposis. Unfortunately, the toxicity of traditional NSAIDs limits their long-term use for cancer prevention.[18]

NSAIDs are inhibitors of the cyclooxygenase enzymes that catalyze arachidonic acid metabolism to the prostaglandins, prostacyclin, and thromboxanes. One isoform, cyclooxygenase-1 (COX-1), is constitutively expressed and appears to mediate several physiologic functions. Not surprisingly, then, inhibition of COX-1 is associated with the common side effects of NSAIDs.[18,19] Another isoform, cyclooxygenase-2 (COX-2), is induced. Cytokines and growth factors seem causally associated with its expression in inflammation and neoplasia.[20-22] Selective inhibition of COX-2, but not of COX-1, appears to reduce gastrointestinal toxicity.[19,23-25] The chemopreventive effects of NSAIDs may be due at least in part to inhibition of COX-2,[26,27] though non-COX-2 mechanisms may be a factor in the chemopreventive effects of both selective and nonselective COX inhibitors.

If NSAIDs inhibit colon carcinogenesis, it is important to determine if their effect occurs through inhibition of the COX-1 or COX-2 isoenzyme or by non-COX processes. Most data support the notion that COX-2 is the critical mediator, though other pathways may also be involved.[26,28,29] It has been established that COX-2 is expressed in colorectal adenomas and carcinomas, both in humans...
and rodents. In familial adenomatous polyposis, COX-2 has been detected in very small adenomas in mice harboring germ-line APC mutations.[21,27,30] COX-2 inhibitors have been shown to decrease the incidence of carcinogen-induced neoplasia in rats and to lower incidence of adenomas in murine APC models.[27,31,32] In one elegant experiment, the presence of the COX-2 gene was found to be associated with adenomas. In a mouse model of familial adenomatous polyposis, knockout of one COX-2 allele decreased adenoma formation, while homozygous deletion resulted in a greatly reduced adenoma burden.[27] This supported the hypothesis that protective action of NSAIDs is due to inhibition of COX-2.

While a role for COX-2 is now clarified, less is known about the intracellular pathways that mediate such effects. COX-2 appears to mediate signaling of mitogenic growth factors. It also seems to downregulate apoptosis.[33-35] In familial adenomatous polyposis, in which apoptosis is decreased, upregulation through COX-2 inhibition ought to be beneficial.[36]

**COX-2 Inhibition in FAP**

The first concrete evidence of a favorable COX-2 impact on human colorectal neoplasia came in our familial adenomatous polyposis adenoma regression trial (Figure 1).[37] In order to establish whether a COX-2 inhibitor could induce regression in the size and/or number of adenomas in familial adenomatous polyposis, investigators at The University of Texas M. D. Anderson Cancer Center in Houston and St. Marks Hospital in London carried out a randomized, double-blind, placebo-controlled study of celecoxib.[25] Of 113 subjects evaluated endoscopically, 28 were ineligible due to insufficient adenoma burden, while one subject each had a rectal cancer and a large sessile adenoma requiring surgery.

Seventy-five patients were initially randomized to oral celecoxib at 100 mg twice daily, to oral celecoxib at 400 mg twice daily, or to a look-alike placebo twice daily for 6 months; the study duration and adenoma regression end point were based on previous trials of sulindac that had shown efficacy.[2-7] Genetic testing for APC gene mutations was performed with a positive result in 90% of subjects. Comprehensive compliance and patient safety monitoring were performed throughout the trial with adverse events graded according to National Cancer Institute (NCI) Common Toxicity Criteria.[38]

Colonoscopy or sigmoidoscopy (if previous colectomy had been done) and duodenoscopy were carried out at baseline and off-study at month 6, immediately upon completion of the 6-month course of drug or placebo. The exams were documented by videotape and a series of photographs. A very involved process was employed to reliably and quantitatively score polyp density. The investigator performing the scoring was not involved in the endoscopy, and was blinded as to treatment arm and as to whether the exam was pre- or post-treatment. This scoring relied on still photographs, though videotapes were employed to resolve ambiguities in the photos.

A second, qualitative scoring system was also employed. A global assessment of the colorectal, rectal (in postcolectomy cases), and duodenal adenoma burden was conducted by each of five endoscopists or surgeons experienced in familial adenomatous polyposis. This was done, in the interest of expediency, during joint videotape-review sessions, though discussion was not allowed during the viewing and sealed scorings were submitted. A score of "better," "worse," or "same" was required in comparing the videos that were presented in random pairs, ie, baseline vs 6 months, and blinded as to temporal sequence and treatment.

Following 6 months of therapy at the highest celecoxib dose, ie, 400 mg twice daily (twice the usual antiarthritic dose), there was a statistically significant ($P = .003$) reduction in adenoma burden compared with baseline, as measured by still photographs in designated regions of interest. Specifically, the high-dose group experienced, on average, a 28% reduction in adenoma count, compared with a 4.5% reduction in the placebo group, and an intermediate reduction of 12% in the 100-mg twice daily group. This effect persisted after adjusting for age, sex, previous surgery (colectomy vs intact colon), baseline polyp burden, and investigating institution.

Applying the more qualitative videotape method of polyp scoring, significant improvement occurred
in the 400-mg group in all colorectal regions. In the low-dose (100 mg twice daily) group, there was a nonsignificant trend toward a treatment response. The celecoxib was well tolerated, with 68%, 56%, and 57% of subjects in the placebo, low-dose, and high-dose groups, respectively, reporting NCI grade 2 or worse adverse event,[38] including diarrhea and abdominal pain. Adverse events requiring subject withdrawal from the trial included suicide (celecoxib 100-mg arm, in a patient with a previous suicide attempt), acute allergic reaction (celecoxib 400-mg arm), and dyspepsia (celecoxib 400-mg arm, though no ulcer was observed on upper gastrointestinal endoscopy). No significant changes occurred in hematologic or chemical profiles.

In the aggregate, these data indicate that COX-2 is an important factor in colorectal carcinogenesis, and that its selective inhibition may retard the formation or progression of adenomas, at least in familial adenomatous polyposis.[26] It remains to be seen whether intervention with COX-2 inhibitors will prevent, or at least delay, the initial occurrence of adenomas in young familial adenomatous polyposis carriers diagnosed with familial adenomatous polyposis. If so, it may become possible to postpone colectomy or proctocolectomy for a period of years, enabling such young subjects to be more active participants in their disease management.

Meanwhile, patients who have already undergone colectomy and who develop recurrent rectal polyps may be treated with celecoxib. Most such patients and their surgeons are eager to avoid a second operation. If celecoxib is to be considered an adjunct to endoscopic polypectomy in such patients, careful attention must be paid to appropriate follow-up. Anecdotal cases of progression to overt malignancy have been documented in subjects treated with sulindac, even as regression of adenomas was documented. Clearly, it is vital that patients must be managed on an individual basis.

At the time celecoxib was being approved for use in familial adenomatous polyposis, the US Food and Drug Administration (FDA) requested that several additional, postmarketing studies be performed. One such investigation was to be a clinical trial of celecoxib to prevent the onset of first adenomas in young, genotype-positive, phenotype-negative adolescents carrying APC gene mutations. Such a multicenter trial has been proposed and is currently under review.

A second FDA-mandated study to describe the clinical benefit of celecoxib would comprise a registry of clinical outcomes in patients with familial adenomatous polyposis. Conceptually, this would entail treating polyp-affected adolescents (12 years or older) with the approved dose of 400 mg twice daily oral celecoxib with an end point of "time to familial adenomatous polyposis-related events" (specifically, familial adenomatous polyposis-related surgery, gastrointestinal cancer, desmoids, or death). These outcomes would be compared with historical, untreated controls. Adverse events would be closely monitored. Preparations are underway for such a multicenter, familial adenomatous polyposis registry-based study.

Another familial adenomatous polyposis trial is opening to accrual at M. D. Anderson Cancer Center and St. Marks Hospital. This will be a two-arm, randomized, prospective, double-blind trial in familial adenomatous polyposis subjects with residual colorectal (no previous colectomy), rectal (postcolectomy), and/or duodenal adenomas (a small group with previous proctocolectomy). Oral celecoxib at 400 mg twice daily will be compared with oral celecoxib at 400 mg twice daily plus difluoromethylornithine at 0.5 mg/m² (rounded to the nearest 250 mg). Target accrual is 152 subjects; endoscopic evaluation will be at 0 and 6 months. The primary end point will be adenoma recurrence, as in the original celecoxib trial. In addition, a region of representative, dense adenoma involvement will be cleared of adenomas at baseline, with measurements taken of adenoma recurrence in that area.

Difluoromethylornithine is an irreversible enzyme-activated inhibitor of ornithine decarboxylase, which in turn is rate-limiting in the polyamine pathway.[39] Although its pathway differs from that of COX-2 inhibitors, it has been shown to decrease carcinogen-induced tumors in rodents.[40] The fact that it uses a different pathway will be advantageous in achieving hoped-for synergy in reducing and preventing adenomas in familial adenomatous polyposis.

**COX-2 Inhibition in HNPCC**
Studies have shown that COX-2 expression occurs in colorectal adenomas and cancers. However, it may not be as great in colorectal adenomas and cancers in hereditary nonpolyposis colorectal cancer as it is in familial adenomatous polyposis sporadic colorectal cancer.[41] In our series,[41] 16 of 24 hereditary nonpolyposis colorectal cancer tumors (67%) and 24 of 26 sporadics (92%) showed evidence of COX-2 immunoreactivity. If confirmed in additional investigations, this would constitute another manner in which the "hereditary nonpolyposis colorectal cancer pathway," characterized by instability in microsatellite markers and a relative paucity of tumor suppressor gene mutations and allelic losses, differs from that of both familial adenomatous polyposis and sporadic colorectal cancer. Further, to the extent that COX-2 is relatively underexpressed, inhibitors of COX-2 ought to be less effective in hereditary nonpolyposis colorectal cancer.

Because of the relatively low incidence of adenomas in hereditary nonpolyposis colorectal cancer, it would be difficult to conduct clinical trials with sufficient statistical power to demonstrate a reduction in adenoma incidence. Nevertheless, we are evaluating the effect of celecoxib on various intermediate markers in hereditary nonpolyposis colorectal cancer. Accrual was recently completed, and included 77 subjects with either a mismatch repair gene mutation or previous microsatellite-instability-positive colorectal cancer in the appropriate family history setting. The study follows a design akin to that used in the first familial adenomatous polyposis trial. The three arms are placebo, celecoxib at 200 mg twice daily, and celecoxib at 400 mg twice daily for 1 year. Subjects undergo colonoscopy at baseline and the off-study exam is carried out at month 12, immediately upon completion of the 12-month course of drug or placebo.

The central feature of the study is evaluation of the presence or absence of COX-2 modulation of markers for apoptosis and proliferation in the normal-appearing mucosa. Indigo carmine spray for mucosal contrast is performed to identify whether any aberrant crypt foci are present. Gross surface characteristics of aberrant crypt foci are evaluated with a magnifying or zoom colonoscope and this is correlated with histology. These aberrant crypt foci will be assessed for COX-2 expression and other markers, including such measures of apoptosis as TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP-biotin endlabeling) staining and caspase activity.[42,43]

**COX-2 Inhibition in Sporadic Colorectal Adenoma**

As noted above, laboratory studies in tumor cell lines and in animal models have demonstrated that COX-2 is important in colon neoplasm formation. Our data from a study in subjects with familial adenomatous polyposis shows that COX-2 inhibition is significantly effective in reducing adenoma burden. However, whether the effect in familial adenomatous polyposis can be extended to the more prevalent problem of sporadic adenoma and cancer of the colorectum remains to be seen. Nevertheless, these data support the conduct of colorectal neoplasm prevention trials in subjects with sporadic, nonfamilial adenomas.

The first large-scale COX-2 inhibitor trial involving subjects with a history of sporadic colorectal adenoma has recently begun (personal communication, M. Bertagnolli, March 2000). This is a phase III, prospective, randomized, double-blind, three-arm, multicenter trial in which celecoxib at multiple doses (200 and 400 mg twice daily) is compared with placebo. Subjects will have undergone endoscopic polypectomy of adenoma (≥ 1 cm, or two or more adenomas of any size) within 3 months of study entry. The primary end point will be recurrence of adenomas at 12 and 36 months following study entry. As in our familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer trials, this sporadic adenoma trial will include measures of surrogate end points in a nested subgroup of subjects. Anticipated enrollment will be 650 subjects per arm (1,950 in total).

**Conclusion**

A considerable volume of preclinical data support the safety and efficacy of COX-2 inhibitors, and several clinical chemoprevention trials will soon provide concrete information about the potential for these agents to prevent both familial and sporadic neoplasia in the colon. Already being explored is the possibility of a chemopreventive role for celecoxib in other organs. One trial to prevent recurrent bladder dysplasia is being led by a team from M. D. Anderson Cancer Center (personal communication, A. Sabichi, June 2000). Other trials are evaluating the effect of celecoxib on Barrett’s
esophagus and actinic keratosis. More detailed information about these trials is available through the NCI website at [www.cancernet.nci.nih.gov](http://www.cancernet.nci.nih.gov)

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