# Old Drug Combo Prevents Colorectal Adenomas

BY BETSY BATES
*Los Angeles Bureau*

SAN DIEGO — Small doses of two historic drugs administered in tandem profoundly reduced the development of colorectal adenomas in patients with prior adenoma formation, heralding a "mid-game home run" in secondary chemoprevention investigators reported at the annual meeting of the American Association for Cancer Research.

Dr. Frank L. Meyskens Jr., professor of medicine and biological chemistry at the University of California, Irvine, presented "late-breaking" results from a phase III trial of difluoromethylornithine (DFMO), a synthetic inhibitor of ornithine decarboxylase, and sulindac (Clinoril), a nonsteroidal, anti-inflammatory drug (NSAID), in 375 patients.

**At 3 years, total adenomas in treated patients were reduced by 70%, advanced adenomas by 92%, and multiple by 95%, compared with those on placebo.**

Patients were recruited following resection of at least one adenoma (greater than or equal to 3 mm) discovered on colonoscopy—a history placing them at significant risk of recurrence. (Subjects were excluded if they had a history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or inflammatory bowel disease.)

Oral doses of DFMO (500 mg) and sulindac (150 mg) daily were given to 191 randomized patients, while 184 were assigned to placebo. Low-dose aspirin were used by approximately 40% of patients in each group.

At 3 years' follow-up, total adenomas detected by colonoscopy were reduced by 70%, advanced adenomas by 92%, and multiple adenomas by 95% in treated patients versus those on placebo. Specifically, an adenoma was found in 42 of 97 patients who received placebo and completed the trial (43%), compared with 12 of 107 on the DFMO/sulindac combination (11%).

Advanced adenomas—large, intramucosal or invasive adenomas containing histologic features associated with conversion to colorectal cancer—were seen in nine (9.3%) patients in the placebo group and one patient receiving combination chemoprevention. More than one adenoma was found in 15 patients receiving placebo versus just 1 patient in the chemoprevention arm.

"These are absolutely stunning findings," Dr. Scott M. Lippman told meeting attendees in a formal discussion of the phase III results. "I would consider this a mid-game home run."

The research culminates a "long quest" by Dr. Meyskens and coinvestigator Dr. Eugene W. Gerner of the University of Arizona, Tucson, to fight the development of cancer by targeting ornithine decarboxylase, a key polyamine pathway that acts as an instigator of growth.

DFMO, long abandoned as chemotherapy because of inefficacy and hearing-related toxicity, was known to prevent many forms of cancer in preclinical and in vitro models. The researchers conducted novel "de-escalation" dose-finding trials, determining in the mid-1990s that a 500-mg dose (one-fiftieth of the therapeutic dose and one-quarter of the ototoxic dose) could reduce the polyamine content of colonic flat mucosa.

The decision was made to combine the drug (approved for African sleeping sickness and, more recently, as a topical depilatory) with sulindac, an NSAID in use for a half-century, to maximize each drug's efficacy at the smallest possible doses.

Sulindac has shown clinical activity against familial adenomatous polyposis (FAP) in vitro and in five preclinical animal models, explained Dr. Meyskens. It has multiple mechanisms of action and was used in the trial at a 150-mg dose daily, half the dose used in the treatment of arthritis.

Adverse events were carefully monitored in the study, with particular attention given to cardiovascular and otologic side effects previously associated with NSAIDs and DFMO.

At least 1 serious adverse event requiring hospitalization was seen in 31 patients receiving placebo and 42 in the DFMO/sulindac group. No significant difference was seen in the number of patients experiencing a serious adverse event (grade III or greater).

Serious cardiovascular side effects occurred in 16 of the patients receiving active treatment versus 9 in the placebo arm. This difference, while not statistically significant, may indicate a "worrisome trend" and deserves further study, according to Dr. Lippman of the M.D. Anderson Cancer Center in Houston, a formal discussant of the study.

No hearing loss was perceived in patients receiving DFMO and sulindac, although a 1-2 dB difference was found in precise hearing tests. This difference is "a sound equivalent to rubbing your two fingers together," perceptible only to "a very alert 17-year-old," or a similar individual, Dr. Meyskens said.

The hearing loss was reversible with discontinuation of the drug.

The DFMO/sulindac drug combination has shown "very promising" results in early studies of prostate cancer and is being studied as a topical agent in skin cancers.

Future research may investigate its chemopreventive potential in patients with "cured" low-stage colorectal cancer, and a larger group of patients with prior advanced adenomas detected at colonoscopy. However, because DFMO has gone off patent, creative solutions are being sought to finance future studies of the drug combination's potential as a chemopreventive agent, Dr. Meyskens said.

The study was published online simultaneously with the presentation at AACR (Cancer Prev. Res. 2008 April [Epub doi: 10.1158/1940-6207.CAPR-08-0042]). ■

# Data Shore Up Celecoxib's Colorectal Chemopreventive Effects

BY FRAN LOWRY
*Orlando Bureau*

SAN DIEGO — Celecoxib reduced the incidence of advanced colorectal adenomas by 41% at 5 years in high-risk patients who took the controversial COX-2 inhibitor for 3 years in a cancer prevention trial before stopping it because of cardiovascular safety concerns.

"Even 2 years after we discontinued treatment with celecoxib, our patients still derived a considerable chemoprotective benefit," Dr. Monica Bertagnolli of Brigham and Women's Hospital, Boston, said at the annual meeting of the American Association for Cancer Research.

Just as notably, Dr. Bertagnolli reported celecoxib (Celebrex) was shown to be safe in patients who had no underlying risk factors for cardiovascular disease when they entered the study.

Dr. Bertagnolli led the Adenoma Prevention With Celecoxib (APC) trial, which began enrolling patients in 1999 and was planned to run for a total of 5 years of drug treatment. Sponsored by Pfizer Inc., the study was designed to test the efficacy and safety of two doses of celecoxib in preventing colorectal adenomas in 2,035 individuals at high risk for colon cancer.

Patients who had adenomas removed before study entry were assigned to placebo (679 patients), 200 mg twice a day of celecoxib (685), or 400 mg twice a day (671) of celecoxib. They were followed with colonoscopies performed at 1 and 3 years. Just as the last patients completed 3 years of the study, the investigators recognized increased cardiovascular toxicity with celecoxib and discontinued the drug in all patients.

"At the time we began our study, the cardiovascular toxicity of celecoxib was not known. In fact, this study was the first to unveil cardiovascular disease risk with the drug. So we did not screen any of our study population for cardiovascular risk factors. Most of our patients—84%—whose median age was 60 at the time of study entry, had at least one risk factor," Dr. Bertagnolli explained in an interview.

The efficacy results at the 3-year point were impressive, she said. Sixty percent of the placebo group had new adenomas, compared with 43% of patients receiving 200 mg of celecoxib twice a day, and 38% of those in the high-dose group receiving 400 mg of celecoxib twice a day The reduction in the rate of new advanced adenomas was even more striking at this point, with a 64% reduction at the lower dose and a 55% reduction at the higher dose of celecoxib, she noted.

Although the patients discontinued celecoxib, Dr. Bertagnolli and her colleagues decided to continue the trial as an observational study. Approximately one-third of the original randomized cohort had a colonoscopy at 5 years as planned, she said. "We kept the study going, and I'm glad we did, because now we have interesting new data," she said.

At 5 years, with no drug on board for 1.5-2 years, the reduction in advanced lesions was 41% in the cohort who received the lower dose of celecoxib and 26% in patients who received the higher dose. There was no rebound effect—that is, lesions did not suddenly appear when the drug was stopped, Dr Bertagnolli said.

"Interestingly, the lower dose of celecoxib was the most effective at the 5-year end point," Dr. Bertagnolli commented.

The investigators also analyzed safety, looking at any event that occurred after patients took the first dose of celecoxib up until 30 days after they took the last dose.

Cardiovascular events (myocardial infarction, stroke, peripheral vascular disease, and vascular therapeutic procedure) rose with the dose of celecoxib, occurring in 3.8% of the patients on placebo, in 6.0% of patients on the low dose of celecoxib, and in 7.5% of patients on the high dose of celecoxib.

The data showed that patients with preexisting risk factors, defined as smoking, hypertension, diabetes, hyperlipidemia, atherosclerotic heart disease, and age over 65 years, had the greatest risk:

► For patients with no cardiovascular risk factors before using celecoxib, the rate of cardiovascular adverse events was 0.9% in the placebo group, 3.9% in the 200-mg b.i.d. group, and 1.9% in the 400-mg b.i.d. group.

► If a patient had one risk factor, the rate was 2.2% in the placebo group, 3.7% in the 200-mg b.i.d. group, and 4.9% in the 400-mg b.i.d. group.

► Among patients who had two or more cardiovascular risk factors at the time they entered the study, those on placebo had a cardiovascular adverse event rate of 5.9%; those on 200 mg b.i.d., 8.2%; and those on 400 mg b.i.d., 11.2%.

This risk needs to be balanced with the benefit patients derived from celecoxib, Dr. Bertagnolli said. "These patients were at very high risk for colorectal adenomas. Twenty-two percent of patients on placebo got advanced adenomas during the 5 years, and over 70% of patients had adenomas that recurred if they were on placebo. So this is a very high-risk group."

She concluded that these new data "allow us to carefully select patients who can benefit from celecoxib. It should definitely be used with caution, but patients with a high risk for colon cancer and a low risk for cardiovascular disease are going to receive a significant benefit."

"Studies such as Dr. Bertagnolli's are reinvigorating this avenue of research, with major implications for public health," said Dr. Scott M. Lippman, professor of clinical cancer prevention at the University of Texas M.D. Anderson Cancer Center, Houston. ■