Old Drug Combo Prevents Colorectal Adenomas

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 non-steroidal, anti-inflammatory drug (NSAID), in 375 patients.

Patients were recruited following resection of at least one adenoma (greater than or equal to 3 mm) detected on colonoscopy—a history placing them at significant risk of recurrence. (Subjects were excluded if they had a history of familial adenomatous polyposis, hereditary non-polyposis 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 by 95%, compared with those on placebo.

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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

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“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 colorectal cancer (CRC) was shown to be reduced in patients who had no underlying risk factors for cardiovascular safety concerns.

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