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), an NSAID, in 375 patients.

Patients were recruited following resection of at least one adenoma (3 mm or larger) discovered on colonoscopy—a history placing them at significant risk of recurrence.

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 was used by approximately 40% of patients in each group.

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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 with histologic features linked 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 and 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 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, with particular attention given to cardiovascular and otologic side effects previously associated with NSAIDs and DFMO.

At least one serious adverse event requiring hospitalization was seen in 31 patients receiving placebo and 42 patients in the DFMO/sulindac group. No significant difference was seen in the number of patients experiencing a serious adverse event.

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

No hearing loss was perceived in patients receiving DFMO and sulindac, although a 1- to 2-dB difference was found in precise hearing tests. This difference is "a sound equivalent to rubbing your two fingers together," Dr. Meyskens said. The hearing loss was reversible with discontinuation of the drug.

The DFMO/sulindac drug combination also 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]). ■

Patient Preference May Affect Adherence to Referrals for Colorectal Cancer Screening

BY KATE JOHNSON
Montreal Bureau

MONTREAL — Primary care physicians referring patients for routine colorectal cancer screening may see better adherence, particularly among men, if they consider patient preference regarding screening modality, reported Maida Sewitch, Ph.D., from McGill University, Montreal. However, the picture is less clear for women.

In a study of 203 primary care patients referred for colorectal cancer screening (40% male, mean age 64 years), overall adherence was 52%, Dr. Sewitch reported in a poster at Canadian Digestive Diseases Week.

For both genders combined, the strongest predictor of adherence was a physician's referral that matched a patient's preferred screening modality (adjusted odds ratio 3.64), she said. However, the results looked quite different when analyzed according to patient gender.

"What we found was that the people for whom matched modality was important were the men—and that men who were matched on modality were 3.5 times more likely to adhere to screening referral than men who were not matched. But women didn't care about modality. We didn't expect that at all," Dr. Sewitch said in an interview.

The four choices of screening modality offered in the study were colonoscopy, double contrast barium enema, flexible sigmoidoscopy, and fecal occult blood testing (FOBT). The most commonly requested modality was FOBT, she said.

Although matching the referral modality to patient preference increased the odds of screening adherence in men (AOR 3.49), it only had a slight impact in women (AOR 1.24), she said. Instead, the predictor of female adherence to screening was past history of screening (AOR 2.1), she reported.

Women may "have more trust in their physician's recommendation, and a past history of screening may demystify the experience, whereas men want what they want," Dr. Sewitch said. "It might have a lot to do with control.

"Physicians should be speaking with patients about what they want. If they're going to recommend some kind of colorectal cancer screening, they can ask their patients what they want to do and give their referral based on that," she said.

A second poster presented at the meeting described an investigation of patient preference regarding the timing of a precolonoscopy consult with a gastroenterologist. A total of 125 average-risk patients (66% male, mean age 60 years) participated in the study, with 21% receiving a gastroenterology consult on a different day (DD) previous to their colonoscopy, and 79% receiving the consult on the same day (SD), just before their colonoscopy.

Patients were asked to complete a questionnaire after their colonoscopy regarding their preference for a DD or SD consult, reported Dr. Liliana Oliveira from the University of Ottawa. The study found that patient preferences appeared to be affected only by prior consultation experience. Among patients who had an SD consult, 86% indicated a preference for this practice, and among those who had a DD consult, 61.5% preferred this practice; these findings were significant.

She stressed that SD consultation is only intended for average-risk patients. Although SD consultation is common, she said it remains somewhat controversial. ■