DFMO may affect Barrett's esophagus

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Pilot study results suggest that difluoromethylornithine can modulate biomarkers of cell proliferation in patients with Barrett's esophagus and mucosal dysplasia.

"While there was a suggestion that DFMO may influence the extent of Barrett's dysplasia, this finding is very preliminary and further study of this agent in a larger number of patients is needed," said Frank A. Sinicrope, M.D., professor of medicine and oncology at the Mayo Clinic, Rochester, MN.

Sinicrope presented his findings here at the American Association for Cancer Research's Seventh Annual International Conference on Frontiers in Cancer Prevention Research.

The single-arm study included 10 patients with Barrett's esophagus and low-grade dysplasia. The patients received 0.5 g/m2/d of DFMO for six months. Using an endoscope, the researchers examined esophageal biopsies at enrollment and at three, six and 12 months (where available). A gastrointestinal pathologist who was blinded to the clinical/biomarker data graded the dysplasia.

Sinicrope conducted this study while at The University of Texas M. D. Anderson Cancer Center. He collaborated with colleagues at the National Cancer Institute, and the Arizona Cancer Center, Tucson.

After six months of DFMO treatment, one patient's dysplasia regressed, one patient's progressed, and eight patients had stable disease. At six

months, two patients in the stable group who started with extensive low-grade abnormal cells had only limited or focal dysplasia based on four or more biopsies. These improvements remained at 12 months.

DFMO lowered the level of the polyamine putrescine, a target of the drug and a possible cancer risk marker. The agent works by inhibiting an enzyme in polyamine synthesis called ornithine decarboxylase (ODC). "ODC activity in Barrett's mucosa has been shown to be significantly higher in Barrett's than in normal adjacent mucosa from the same patients," Sinicrope said. "Since DFMO inhibits polyamine synthesis, the fact that putrescine levels were decreased at six months and later returned to baseline after being off the drug for six months suggests that the drug is affecting its target."

Interestingly, DFMO also reduced expression of Kruppel-like factor 5 (KLF5) gene, an important marker of abnormal cell proliferation in the esophagus that may represent a novel drug target.

"The results are encouraging because they identify KLF5 as a potential target of DFMO, which suggests a potential mechanism contributing to the chemopreventive effects of DFMO," Sinicrope said. "KLF5 has been shown to regulate proliferation, apoptosis and invasion in esophageal cancer cells."

Generally, DFMO was well tolerated. One patient had hearing loss and balance-related problems related to treatment.

"DFMO warrants further evaluation as a chemopreventive agent in patients with Barrett's esophagus and mucosal dysplasia," Sinicrope said. Currently, the Mayo Clinic researcher and his colleagues are planning a placebo-controlled chemoprevention trial in this patient population.

Source: American Association for Cancer Research