Vit. D May Have a Role in Preventing Colon Cancer

BY FRAN LOWRY
Orlando Bureau

SAN DIEGO — Calcium and vitamin D supplementation may protect against colorectal cancer by creating an environment in the colon that is less conducive to the formation of polyps and adenomas.

In a pilot study presented in a poster at the annual meeting of the American Association for Cancer Research, subjects who took 800 IU of vitamin D_3 per day for 6 months increased the expression of Bax—a protein that promotes the killing of damaged cells—in their colons by 56%, compared with subjects who took placebo.

When calcium was added to the vitamin D, Bax expression also increased, but to a lesser extent (33%), reported Veronika Fedirko, a PhD candidate at Emory University's Rollins School of Public Health, Atlanta.

"We were interested in how calcium and vitamin D prevent colorectal adenomas and colorectal cancers. There is pretty good evidence for calcium, but not as much for vitamin D," Ms. Fedirko said in an interview.

Ms. Fedirko and her colleagues randomized 92 patients aged 40-75 years with a history of at least one adenomatous colonic or rectal polyp within the past 36 months to receive one of the following treatments for 6 months: 2,000 mg calcium a day (23 patients); 2,000 mg calcium plus 800 IU vitamin D a day (23); 800 IU vitamin D a day (23); or placebo (23).

Patients underwent a colorectal biopsy at study entry and another biopsy at the end of the study period. The tissue samples were examined for expressions of Bcl-2, an apoptosis inhibitor, and Bax, an apoptosis promoter.

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After 6 months, Bax expression along the full lengths of the colorectal crypts rose by 56% in the vitamin D–alone group, and by 33% in both the calcium alone and calcium-plus–vitamin D groups, relative to the placebo group. The vitamin D treatment effect was more pronounced in the upper 40% of the crypts.

There were no statistically significant treatment effects on Bcl-2 expression, although data indicated a potential decrease in Bcl-2 expression after supplementation with calcium alone and with calcium plus vitamin D, said the researchers. They also looked at the ratio of Bax to Bcl-2 density as an indicator of the balance of pro-apoptotic versus anti-apoptotic stimuli in the colorectal crypts. They found that the ratio of Bax to Bcl-2 increased 62% in the calcium group, 47% in the vitamin D group, and 71% in the calcium-plus–vitamin D group.

For the vitamin D group, the proportional increase in the Bax to Bcl-2 ratio in the upper 20% as opposed to the lower 20% of the crypts was 352%, compared with placebo. "It appears that the strongest treatment effect was due to vitamin D and that this occurred in the upper sections of the colon crypts," Ms. Fedirko said.

Cells that reach the top of the colon crypt are more likely to be diseased or to have mutations, and are therefore prime candidates to be killed off, Ms. Fedirko explained. The fact that vitamin D enhanced Bax production is therefore encouraging, she said.

"Our patients already had adenomas; they have something in their colon that is not right, so supposedly they have a low rate of apoptosis to start with. If we give them vitamin D, and if this increases the level of apoptosis, they will have fewer cells that will ever get to the top of the crypt, so they will be less likely to develop adenomas," said the researchers. ■

KRAS Mutation in Colon Ca Blocks Cetuximab

BY MARY ELLEN SCHNEIDER
New York Bureau

CHICAGO — Colorectal cancer patients whose tumors contain the wild-type KRAS gene responded better to treatment with cetuximab plus chemotherapy than did patients with tumor KRAS mutations, according to data presented during a plenary presentation at the annual meeting of the American Society of Clinical Oncology.

More patients with wild-type KRAS tumors responded to cetuximab (Erbitux) plus the FOLFIRI (leucovorin, fluorouracil, and irinotecan) chemotherapy regimen (59%) than to FOLFIRI alone (43%), reported Dr. Eric Van Cutsem, the lead study author and professor of medicine at the University Hospital Gasthuisberg in Leuven, Belgium. The findings are based on a further analysis of data from the Cetuximab Combined with Irinotecan First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) trial, which was presented at last year's ASCO meeting.

The original CRYSTAL trial data indicated that metastatic colorectal cancer patients who received a combination of cetuximab and FOLFIRI had a 15% reduced risk of disease progression. The researchers subsequently asked why some patients benefited from the regimen and others did not, Dr. Van Cutsem said.

In an effort to answer this question, they performed a retrospective analysis of the intent-to-treat population of the CRYSTAL trial. Using archived tumor material, the researchers were able to perform quantitative polymerase chain reaction–based KRAS mutation analysis of codons 12/13 for 540 patients from among the original 1,198 patients included in the trial. The research team disclosed receiving research funding from Merck & Co. and other financial relationships with the company, which markets cetuximab outside the United States and Canada.

KRAS tumor mutations were detected in about 35% of patients; about 65% of patients had KRAS wild type tumors. There were no significant differences in the baseline demographics between the wild-type KRAS tumor patients and the mutant KRAS group, Dr. Van Cutsem said.

Among the patients with wild-type KRAS tumors compared, the researchers found a significant benefit in favor of the cetuximab-FOLFIRI combination, compared with treatment with FOLFIRI alone. There was a 32% decreased risk for disease progression (hazard ratio 0.68) for combination therapy, which was statistically significant.

The median progression-free survival was 8.7 months for KRAS wild type patients treated with FOLFIRI only and 9.9 months for KRAS wild type patients treated with cetuximab plus FOLFIRI. In addition, among KRAS wild type patients, the progression-free survival rate at 1 year was 25% for FOLFIRI alone and 43% for the cetuximab-FOLFIRI combination.

Cetuximab made no difference in progression-free survival for the mutant KRAS population. "The benefit here was confined to the patients with the KRAS wild type tumor," Dr. Van Cutsem said.

The evaluation of patient response to treatment, a secondary end point of the study, revealed that 59% of wild-type KRAS patients responded to treatment with cetuximab and FOLFIRI, compared with 43% of patients who responded to FOLFIRI alone. There was no significant difference in overall response between the treatment groups for patients with KRAS mutations.

The researchers also analyzed side effects and found no new signals of toxicity.

The results are consistent with previous research findings, Dr. Van Cutsem said. Several retrospective studies have shown that benefit from cetuximab was confined to KRAS wild type patients. Those with mutant tumors do not benefit from anti–epidermal growth factor receptor antibodies, these studies have found. "The data we report here today are in agreement with the biolog."

Given the predictive value of the KRAS gene, Dr. Van Cutsem recommended that KRAS testing should become part of routine clinical practice. By knowing in advance if there is a KRAS mutation, physicians can avoid exposing patients to the unnecessary side effects of a treatment that will not be effective, he said.

KRAS testing should be fairly simple for clinicians, he said, because they can do it using archived tumor samples without performing fresh biopsies. Effective polymerase chain reaction–based assays are already commercially available.

Routine use of KRAS testing also got some recent support in Europe when the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion on Merck's application to expand the use of cetuximab. The committee recommended the use of cetuximab in patients who have metastatic colorectal cancer with KRAS wild type tumors. The recommendation was for use in combination with chemotherapy and alone in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

The results of the CRYSTAL trial analysis, combined with other recent studies that point to the predictive value of KRAS mutation status, support routine KRAS testing for patients with metastatic colorectal cancer who are being considered for treatment with epidermal growth factor receptor inhibitors, Dr. S. Gail Eckhardt, head of medical oncology at the University of Colorado Cancer Center in Aurora, said during a discussion.

However, more research is needed to see if these results are applicable in other diseases where epidermal growth factor receptor inhibitor therapy is being used, she said. ■

Kids Born With Hernia Must Be Tracked Closely

PHOENIX — Children with congenital diaphragmatic hernia are likely to have long-term health problems requiring close, long-term follow-up, Dr. Tim Jancelewicz said at the annual meeting of the American Pediatric Surgical Association.

Dr. Jancelewicz, of the University of California, San Francisco, and his colleagues reviewed 357 clinic visits made over a 10-year period by 90 patients with congenital diaphragmatic hernia (median follow-up 4 years). Of those, 8% required extracorporeal membrane oxygenation (median 15 days). Initial patch repair was done in 57%, and 36% have had recurrence of the hernias.

The children underwent neurodevelopmental assessment, which identified normal neurodevelopmental outcomes in 55% of the cohort. Another 13% had suspect disease, 24% had confirmed abnormal outcomes, findings for 8% were undetermined.

Four factors significantly predicted neurodevelopmental delay: liver herniation at birth, initial patch repair, intubation for at least 15 days, and discharge home on oxygen. Neurodevelopmental delay was seen in 59% of those with liver herniation, 60% of those with initial patch repair, 67% of those with at least 15 days of intubation, and 82% of those who were discharged on oxygen.

All of the children had hearing assessments; only 46% had normal hearing. Two factors, initial patch repair and intubation of at least 15 days, significantly predicted hearing loss. Of those with an initial patch repair, 43% had hearing loss. None of those who had a primary repair had hearing loss. While 44% of those with more than 15 days of intubation developed hearing loss, 95% of those with less than 15 days of intubation had normal hearing.

—Michele G. Sullivan