Colon Cancer Prevention: From Prophylaxis in UC Patients to Adequate Bowel Preparation for Colonoscopy

Chicago - New data are providing guidance for further improving already important strategies for the prevention of colorectal cancer. As demonstrated here at DDW, in one series of studies, the effort to isolate a therapeutic mechanism which reduces cancer risk in patients with ulcerative colitis has provided several new molecular targets to expand pathways of chemoprophylaxis. Perhaps the most important finding for clinical practice is that the molecular suppression of cancer pathways depends on continued mesalamine exposure. Concurrently, progress in defining the key characteristics of adequate bowel preparation appear destined to substantially and perhaps dramatically reduce the risk of missed neoplasia, providing one of the most important opportunities to lower colorectal cancer rates. The key clinical message from these studies is that while bowel preparations are not necessarily interchangeable for efficacy, they should now all be administered on a split dose schedule.

New opportunities for reducing colon cancer risk have been identified in 2 disparate sets of studies presented here at DDW. In one, the focus is on chemoprophylaxis in patients with ulcerative colitis (UC), where the lifetime risk is almost 6 times that of the general population. Investigators have attempted to isolate mechanisms by which mesalamine provides cancer protection, revealing potentially targetable molecular events. Continuous mesalamine exposure appears critical for protection. In another set of studies, split dosing of a bowel preparation was found to substantially improve quality of the examination. Both groups of studies have immediate relevance for clinical practice.

“The main result of our study is that mesalamine has a profound effect on a gene array implicated in inflammation and change in cell cycle kinetics, both of which are implicated in oncogenic pathways. However, we also document that these effects are transient,” reported Dr. Manisha Bajpai, Robert Wood Johnson Medical School, New Brunswick, New Jersey. As a result, while the new data provide insight into the molecular mechanisms of cancer protection, the key clinical message is that sustained long-term treatment with 5-ASA (mesalamine) is necessary to maintain protection.

Continuous Therapy Inhibits Oncogenic Pathways

There is now a broad array of data associating mesalamine with protection from cancer, but the anti-cancer mechanisms have been unclear. In this gene array study, the exposure of a colorectal cancer cell line to mesalamine appeared to confirm an effect on an array of genes previously suspected of mediating inflammation and oncogenic effects. These included the genes CCNE1, CDC25A and CHEK2. While the study implicated suppression of interleukin-8 (IL-8) as an anti-inflammatory mechanism of mesalamine, mesalamine was also shown to have an anti-proliferative effect by enhancing sensitivity of colon cells to FAS-mediated apoptosis. While the effect was transient, there was a cumulative effect on the target genes with repeated doses.

“On a molecular basis, these studies support the clinical observation that sustained, long-term treatment with 5-ASA is necessary to maintain the anti-cancer effect,” reported Dr. Bajpai, who has also been evaluating potential biomarkers of colon cancer risk and the efficacy of mesalamine in providing protection. One of these, called TC22, is not only expressed in essentially all colon cancers but in almost all polyps with severe dysplasia. It is only expressed in 35% of adenomatous polyps, and it is not expressed in normal colon epithelium. Like the favourable effect on the gene array, mesalamine also produced a persistent reduction in TC22 expression.

“Repeated treatment of the cells with 5-ASA every 24 hours was effective in maintaining suppression of TC22 when compared to control cells, but TC22 expression returned when the mesalamine was stopped,” Dr. Bajpai told delegates. He maintained, “Measurement of TC22 may be a useful clinical tool as a single biomarker in colonoscopic biopsies to assess colon cancer risk and the efficacy of mesalamine’s chemopreventive action.”

Another study by a different set of investigators isolated a further pathway by which mesalamine appears to control cancer growth. In this study, mesalamine was found to inhibit PAK-1, which increases cell adherence, and to prevent tumour cell migration. The lead author of this study, Dr. Vineeta Khare, Medical University of Vienna, Austria, emphasized that the PAK-1 findings do not compete with other potential pathways of cancer prevention, such as those described by Dr. Bajpai.

“We do not maintain that this is the only pathway or even the key pathway by which mesalamine protects UC patients from malignant transformation. However, this pathway, like others, is potentially important because it could identify new targets for intervention,” Dr. Khare explained.

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In this study, microarray analysis was again employed to compare the gene expression profile of colorectal cancer cell lines exposed to mesalamine relative to those not exposed. Mesalamine was found to inhibit 3 tumour-promoting pathways, including MAP kinase signalling, and PAK-1. While all are potentially relevant to an anti-cancer effect, the significant inhibition of E-cadherin, which mediates cell adhesion, correlates particularly well with clinical observations. “We think an anti-adhesion effect can help localize abnormal cell growth, preventing the proliferation that is so critical to cancer development,” Dr. Khare explained.

The evidence that continuous mesalamine is needed to provide protection against colon cancer is supported by clinical observations, which have far more strongly associated present use of mesalamine with cancer protection than history of use. On this basis, several experts have suggested that mesalamine, which is well tolerated, be maintained even when patients have progressed to more aggressive therapies, such as biologics. The reduction in the risk of cancer is a primary motivation for those who advocate this approach.

**Split Dose Bowel Preparation for Improved Colorectal Cancer Screening**

The most recent key advance in colorectal cancer screening is the large body of evidence that demonstrates the superiority of split dosing, which involves taking one half of the dose the night before the colonoscopy and the other half 4 hours before the procedure, when compared to a single dose taken the day before the procedure. The most recent evidence was generated by a randomized controlled trial with Pico-Salax® (picosulfate sodium/magnesium oxide/citric acid [PSMO]). In this study, Dr. Jennifer A. Flemming, Gastrointestinal Diseases Research Unit, Kingston General Hospital, Queen’s University, Ontario, served as senior author. Some 222 patients were randomized to the traditional arm of 1 sachet taken at 5 pm and 1 sachet at 10 pm the night before the colonoscopy, and those in the split-dose arm took 1 sachet the night before at 7 pm and a second sachet 4 hours prior to their colonoscopy. The primary outcome was the quality of the bowel preparation as determined by the Ottawa Bowel Preparation Scale (OBPS).

The difference in the OBPS was highly significantly different (4.05 vs. 5.51; P<0.001) in favour of the split dose, according to Dr. Flemming. There were no significant differences in important safety measures, such as renal impairment or potassium or magnesium levels.

The importance of this advantage was highlighted in a separate study of 373 patients with poor, inadequate or unsatisfactory bowel preparation. Of the 133 patients who underwent a repeat colonoscopy, 34% had at least one adenoma detected and 18% had multiple adenomas or at least one adenoma of at least 1 cm. Presented by Dr. Reena V. Chokshi, Barnes Jewish Hospital, Washington University School of Medicine, St. Louis, Missouri, these data are part of a growing body of evidence that much more rigorous bowel preparation is needed.

“Good is just not good enough,” remarked Dr. Lawrence Cohen, Mount Sinai School of Medicine, New York City. Based on studies like the one performed with PSMO, he characterized split-dose regimens as “the standard of care.” He cautioned that studies repeatedly show that about 25% of bowel preparations are inadequate, and these are almost certainly causing neoplastic tissue to be missed. He noted that, contrary to popular belief, the vast majority of patients will comply with split-dose regimens when told that better bowel preparation will improve the chances of finding occult malignancy.

There are few trials directly comparing the different types of bowel preparation, but the PSMO preparation has been among the most popular in Europe and Canada. This may relate to tolerability as well as efficacy, which is also an important factor in adherence to the bowel preparation regimen.

**Summary**

Due to the frequency with which colon cancer is not first detected until it has reached an advanced stage, prevention is an essential goal. While mesalamine is effective in producing symptom control and healing of mild to moderate UC, its role in preventing UC-related cancer spans across all grades of this disease. Efforts to isolate the specific anti-cancer activities on a molecular basis suggest that continuous therapy is needed to achieve this benefit. Similarly, colonoscopy is an effective tool for early detection of cancer but it is dependent on adequate bowel preparation. A randomized, controlled trial with split dose PSMO confirms large differences in the ability to visualize abnormal tissue.