

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Colorectal Cancer in Focus

Bisphosphonates in Colorectal Cancer



Paul J. Limburg, MD
 Professor of Medicine
 Division of Gastroenterology
 and Hepatology
 Division of Preventive,
 Occupational, and Aerospace
 Medicine
 Mayo Clinic
 Rochester, Minnesota



Siddharth Singh, MBBS
 Instructor of Medicine
 Division of Gastroenterology
 and Hepatology
 Mayo Clinic
 Rochester, Minnesota

H&O What types of strategies have been examined for the chemoprevention of colorectal cancer?

PL Numerous drug agents and drug classes have been evaluated as chemopreventive compounds for colorectal cancer prevention. The most widely studied are probably the nonsteroidal anti-inflammatory drugs and cyclooxygenase (COX)-2 selective inhibitors. Nonsteroidal agents, including aspirin and ibuprofen, appear to have a beneficial effect based on data primarily from observational studies, but also from preclinical studies and randomized controlled trials. The challenge has been that they also have some fairly significant side effects, such as gastrointestinal bleeding. At the population level, nonsteroidal agents and selective COX-2 inhibitors are not recommended for chemoprevention alone. They may be used in some select indications; for example, clinicians may offer a patient the option of taking aspirin to prevent heart disease, and prevention of colorectal cancer may be another benefit of such an intervention.

Other compounds that have shown some potential in the prevention of colorectal cancer include statins and oral antidiabetic agents. At present, these agents are not routinely applied for chemoprevention in clinical practice.

H&O How widely used are bisphosphonates?

PL Bisphosphonates are fairly widely utilized. Between 2005 and 2009, more than 150 million outpatient prescriptions were recorded for bisphosphonates. They are primarily used by postmenopausal women to prevent or reduce the risk of osteoporotic fractures.

H&O How are bisphosphonates thought to affect angiogenesis, cancer cells, and the tumor microenvironment?

SS Bisphosphonates act by inhibiting farnesyl pyrophosphate synthase, the key enzyme in the mevalonic acid pathway. The downstream effect of inhibiting this enzyme is inhibition of the generation of isoprenoids, which are important in posttranslational modification of the small guanosine triphosphate-binding proteins Rab, Rac, and Rho—important mediators of cell growth.

Additionally, bisphosphonates stimulate the production of certain molecules that promote cell death. They also have immunomodulatory effects, and, as a result, they can modify the tumor microenvironment. They inhibit cells called the *tumor-infiltrating macrophages*, thereby preventing macrophage-induced angiogenesis mediated by vascular endothelial growth factor (VEGF).

H&O What prompted your recent meta-analysis on bisphosphonates in colorectal cancer?

SS Over the past 5–7 years, there has been an increasing recognition that bisphosphonates may have beneficial effects in prevention of cancers. These effects have been most widely studied in breast cancer. Some recent studies have suggested that bisphosphonates may be protective against colorectal cancer, whereas other studies have been more ambiguous. In our meta-analysis, we were able to address this question in a more systematic manner looking at all the available data.

H&O What was the study design?

SS We conducted a comprehensive search of all published literature as well as abstracts that were presented at important national and international meetings in gastroenterology and oncology over the past 25–30 years. We identified 6 population-based observational studies that had examined the relationship between bisphosphonate use and colorectal cancer risk. We then appraised the quality of the available data. Subsequently, through meta-analysis, we were able to calculate a summary estimate to analyze the overall risk reduction seen with bisphosphonate use.

H&O What were the study results?

SS There were more than 20,000 cases of colorectal cancer in approximately 392,000 study subjects. The patients receiving bisphosphonates had a 17% lower risk of colorectal cancer than patients who had never received them, after accounting for different confounding factors. When we restricted analysis to 4 studies that consisted of postmenopausal women, the risk of colorectal cancer was 16% less in those receiving bisphosphonates. The risk reduction associated with bisphosphonates was seen in both proximal and distal colon cancer, as well as rectal cancers.

H&O Was there a duration-response effect?

SS Four of the studies reported a duration-response effect. In the meta-analysis, we identified a trend toward a duration-response effect, although this did not reach statistical significance. Risk was reduced by 21% among patients who had used bisphosphonates for more than 3 years versus 13% among patients who had used them for 1–3 years. A significant reduction in risk was not seen in patients who had received bisphosphonates for less than 1 year.

Another group that had studied the effect of bisphosphonates in colorectal cancer reached a simi-

lar conclusion. Thosani and colleagues observed that patients who had used bisphosphonates for more than 1 year had a clinically significant decrease in colorectal cancer risk, whereas patients who had used bisphosphonates for less than 1 year had no significant reduction in risk.

H&O Did different bisphosphonates have different effects?

SS The available studies were limited in answering that question. The most common bisphosphonate in most of these studies was alendronate, which has been the longest available of these agents. However, we anticipate that the risk reduction is a class effect, as opposed to a function of a specific agent of this class. We believe that all bisphosphonates would have a modest chemopreventive effect.

H&O What were the limitations to your study?

SS The current evidence that we have is based primarily on observational studies. Observational studies have some inherent limitations because the study subjects are not randomized to receive the medication. Our biggest concern was that because bisphosphonate users may be more likely to adopt a healthy lifestyle and cancer preventive measures, the observed benefits may be overestimated. Also, bisphosphonate users are more likely to take calcium and vitamin D, which may have independent chemopreventive effects against colorectal cancer and could have confounded the association that we observed in our study. Hence, what is perceived as a bisphosphonate-mediated effect may indeed represent a sum of events and interactions which modify colorectal cancer risk in these patients.

H&O How can your study findings best be applied to clinical care?

PL Due to the limitations of a meta-analysis, our findings require further confirmation in randomized clinical trials. Having said that, I do think there may be implications for clinical care. In women who are on the borderline for receiving bisphosphonate therapy to prevent osteoporotic fracture, the reduction in colorectal cancer risk may be another factor to consider, particularly if there is a strong family history of colorectal cancer. The benefits we observed are worth further investigation both in chemoprevention trials that examine cancer outcomes and in osteoporosis trials that are using these bisphosphonate drugs, where reduction in colon cancer risk can be a secondary endpoint.

H&O Is there any other promising research in this area?

PL Chemoprevention is a field that has been around since the 1970s. There are relatively few drugs approved for chemoprevention by the US Food and Drug Administration because it is difficult to study large numbers of relatively healthy individuals who may have some increased risk for various types of cancers. There have been some agents approved in breast cancer and colon cancer, for example, in individuals with genetic syndromes. The momentum is continuing to build. The interest in chemoprevention research is high at the National Cancer Institute and in the scientific community. We are part of a consortium involving approximately 30 centers across the United States, Canada, and the United Kingdom that is conducting early-phase chemoprevention trials for colon cancer and other malignancies. We hope that successful trials will lead to better ways to reduce cancer risk in the general population.

Suggested Readings

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- Pazianas M, Abrahamson B, Eiken PA, et al. Reduced colon cancer incidence and mortality in postmenopausal women treated with an oral bisphosphonate-Danish National Register based cohort study. *Osteoporos Int.* 2012;23:2693-2701.
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- Singh H, Nugent Z, Demers A, et al. Exposure to bisphosphonates and risk of colorectal cancer: a population-based nested case-control study. *Cancer.* 2012;118:1236-1243.
- Singh S, Singh AG, Murad MH, Limburg PJ. Bisphosphonates are associated with reduced risk of colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2013;11:232-239.
- Whitaker M, Guo J, Kehoe T, Benson G, et al. Bisphosphonates for osteoporosis—where do we go from here? *N Engl J Med.* 2012;366:2048-2051.

Erratum

The March 2013 issue of *Clinical Advances in Hematology & Oncology* omitted changes from Matthew P. Goetz, MD, for his update on CYP2D6 and tamoxifen, which appeared in the Drug Development column. The corrected column, which can be found online at <http://www.hematologyandoncology.net>, includes the following clarification:

H&O What are the current recommendations for breast cancer patients with decreased CYP2D6 metabolism or who are poor metabolizers of CYP2D6?

MG The National Comprehensive Cancer Network (NCCN) guidelines recognize the importance of CYP2D6 enzyme activity, and recommend that patients should avoid potent CYP2D6 inhibitors while taking tamoxifen. However, these guidelines do not recommend that patients be tested for CYP2D6 genetic polymorphisms (the most important reason for altered CYP2D6 enzyme activity).