

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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IN FOCUS: Colorectal Cancer

Reducing the Risk of Recurrent Colon Polyps

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H&O What factors influence the risk of colon polyp recurrence?

EG The simplest factor is age. People over the age of 50 have an approximately 40–50% chance of developing a colon polyp. Due to this evidence, the American Gastroenterological Association (AGA) and the American Cancer Society recommend that this subset of people be screened for colon polyps. Once a patient who is 50 years or older is found to have a polyp, there are a number of important factors in terms of determining whether they are at high risk. Family history is probably the number one contributing factor.

It is said that approximately half of the patients who have had a colon polyp, which is approximately half of the age 50+ population, will recur with another polyp within 3 years. Of those patients, approximately 10% will recur with an advanced polyp or with multiple polyps. Morphologic/pathologic features such as size—a polyp that is greater than 1 cm in diameter is a bad risk factor—indicate an advanced polyp. Individuals who recur with risky polyps have an elevated risk of developing colon cancer.

H&O In terms of diet, what can a patient do to reduce recurrence risk?

EG Patients who are in an elevated risk category of cancer because of a family history should consider some kind of intervention (ie, chemoprevention). For patients that are under the age of 50, diet (higher intake of bran, fruits, and vegetables; taking supplements) and the amount of

exercise can certainly influence the risk of developing a colon polyp, and ultimately, colon cancer. However, if a patient already had a polyp or colon cancer, clinical studies performed by our group, along with studies done by Dr. John Baron and Dr. Arthur Schatzkin, suggest that dietary interventions are not effective in reducing the risk of polyp recurrence.

According to Dr. Baron's group, calcium is one dietary intervention that is associated with a reduced risk of recurrent polyps. The group did a randomized study of dietary calcium and found a 25% reduction in the risk of recurrence. Although calcium may be easily accessible to many patients, it has also been associated with a risk of developing other types of cancer, specifically prostate cancer. Therefore, calcium may not be the best preventative choice for men with recurrent polyps. Furthermore, the magnitude of calcium's effect in women is such that it does not change recommendations for surveillance colonoscopies or screening that would follow polyp or colon cancer removal.

H&O What is the rate of recurrence? Is the presence of polyps a strong indicator of colon cancer?

EG The average annual rate of recurrence in patients who are over 50 years of age and who have a polyp but no history of colon cancer is between 10% and 15% per year. After approximately 3 years, the rate is 35–50%, as documented by numerous intervention studies. For patients who have had colon cancer, the rate of polyp recurrence is higher.

Polyps are an intermediate in at least some colon cancers. From a historical perspective, there are significant data that suggest that if polyps are removed, the risk of colon cancer is reduced. In a recent study, Dr. Nancy Baxter and colleagues found that colonoscopies do not predict colorectal cancer-specific death from right-sided polyps. There are several reasons for this observation, including the possibility that right-sided lesions are more

biologically aggressive. The size and pathologic features of the polyp—the appearance of cells and the shape of the polyp itself (eg, flat or elongated)—all contribute to the likelihood that those polyps will develop into colon cancer; however, genetics and family history are the main indicators for colon cancer.

H&O What role do surveillance guidelines play in the treatment of colon polyps and prevention of cancer?

EG The surveillance guidelines that are put forth by the AGA and the American Cancer Society are published every year. Interpretations of the guidelines that outline the annual changes in the recommendation are published in various journals, such as *Gastroenterology*. For a patient who has early-stage colon cancer or local colon cancer for which the cancer has been removed and the colon is intact, the guidelines suggest that the patient have a surveillance colonoscopy after treatment within 3 years. For an individual who has had a colon polyp but not cancer, the guidelines suggest another follow-up colonoscopy within 5 years if the size of the polyp is less than 1 cm. However, some gastroenterologists recommend an even longer period of time. If a patient had a large polyp, a risky polyp, an advanced polyp, or several polyps, the recommendation is a surveillance colonoscopy within 3 years. Even though the recommendations for surveillance are listed at 3 years, real-life practice actually favors more frequent colonoscopies. Because of this, there is an ongoing debate regarding the overuse of colonoscopies. Many patients will get a surveillance colonoscopy after treatment for colon cancer within 1 year and then annually, as a way to attempt to identify any recurrence at an early stage. Parenthetically, the issue of trying to bring recommendations for surveillance colonoscopies in line with the practical use of surveillance colonoscopy is one major potential application of chemoprevention.

H&O Can you discuss the DFMO/sulindac combination study that you were involved with?

EG The remarkable finding was that the intervention was extremely effective; the study showed a 70% reduction in total polyps. Three years of daily oral doses of difluoromethylornithine (DFMO) and sulindac (at low doses) were effective in reducing the recurrence of risky polyps (polyps that are large and multiple by over 90%).

Another impressive finding was that the study had no statistically significant toxicities. However, the patient population was relatively small (n=375). There have been some new developments in adverse events, some of which have been recently published and some which are

undergoing review for publication. The nonsteroidal anti-inflammatory drug (NSAID) that was used in the study, sulindac, inhibits cyclooxygenases. In the coxib trials that have been done in chemoprevention, it was noted that there was a low but finite rate of serious cardiovascular toxicities. In our study, we had no statistically significant difference in cardiovascular toxicities between treatment arms; there were no deaths, but there was a trend toward increasing cardiovascular events. Subsequent research performed by Dr. Jason Zell included an evaluation of the baseline cardiovascular risk factors of the patients in our trial. In this evaluation, Dr. Zell found that the trend toward increasing cardiovascular toxicity in our treatment group was very closely associated with baseline cardiovascular risk factors. Some NSAIDs alone are associated with cardiovascular risk, but when given to patients who have risk factors for cardiovascular disease before ever receiving these NSAIDs, the risk is higher. Because of the cardiovascular concern, researchers are looking closely at cardiovascular risk factors of patients before they begin to administer an NSAID to determine if a patient is a good candidate for chemoprevention using this type of agent.

We also performed quantitative audiometry at the end of our trial because the main toxicity of DFMO is hearing loss. It was found that at the studied dose, there was a nonclinical but statistically significant toxicity (ie, patients were not aware of the hearing effects of the drug). This is a concern because over time this could present itself as a potential problem for patients. Some progress has been made in this area; a genetic feature has been identified, which can be detected with a blood test, which identifies the subset of patients who are at risk for hearing loss.

Moving forward, the focus is on optimizing the risk benefit consideration by doing trials in patients with elevated risk for colon cancer, and then counseling those individuals on adverse events, especially related to cardiovascular and hearing toxicities.

H&O Are there any subsequent trials studying this combination therapy?

EG One trial that we are planning is a trial that is going to be led by Dr. Zell in patients with prior colon cancer; it will evaluate the DFMO/sulindac combination. The second study for which we are actively providing counsel is a study that is going to be conducted by several of our colleagues in patients who have not had colon cancer, but have had prior risky polyps (ie, large and/or multiple polyps). This study will administer DFMO and an as yet undetermined NSAID.

Our preclinical studies indicate that other NSAIDs, including aspirin, are equally effective in preventing polyps in combination with DFMO and may actually

be safer. Aspirin is a relatively safe NSAID compared to some of the coxibs, which have an associated cardiovascular toxicity. Aspirin use has been associated with gastrointestinal ulcers and tinnitus, especially at high doses. This kind of combination is probably going to be applicable in other cancers, and we are working with groups around and outside the United States who are interested in testing this hypothesis.

H&O Is combination therapy the preferred treatment compared to single-agent therapy?

EG Yes, combination therapy is the preferred treatment. It has been proven that, in general, combination chemotherapy is much more effective than monotherapy for cancer. The reasoning lies in that neoplasia preceding cancer and cancer itself are associated with a number of genetic and biochemical changes in the cells. Expecting that intervention with a single agent is going to be effective in inhibiting the processes associated with carcinogenesis is not a strong clinical argument, nor has it been a strong argument based on the interpretation of clinical trials that have been done either for recurrent polyps or for treatment of colon cancers.

Researchers are evaluating combination therapy in this particular setting and are very interested in including DFMO as they move forward, although all combinations may not include DFMO. Our basic and clinical translational studies have highlighted the importance of the polyamine pathway in cancer. Ornithine decarboxylase is the first enzyme in the synthesis of the group of molecules called polyamines, and DFMO is an irreversible inhibitor of that enzyme. NSAIDs have also been found to attack parts of polyamine metabolism, but at different points than DFMO. There are other metabolic pathways, in addition to the polyamine pathway, that are important in carcinogenesis. Combinations that are going to work either between pathways or within a given pathway are going to be successful, whereas single-agent approaches are not going to be sufficient in most cases.

Suggested Readings

Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med.* 2009;150:1-8.

Zell JA, McLaren CE, Gerner EW, Meyskens FL. Ornithine decarboxylase (Odc)-1 gene polymorphism effects on baseline tissue polyamine levels and adenoma recurrence in a randomized phase III adenoma prevention trial of DFMO + sulindac versus placebo. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2008;26:1502.