

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Chemoprevention in Barrett Esophagus

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G&H What is the current understanding of the pathogenesis of esophageal adenocarcinoma, and how does it differ from that of squamous cell carcinoma?

NB The most common risk factor for adenocarcinoma of the esophagus is gastroesophageal reflux disease (GERD). Other risk factors include increased body mass index. Less common risk factors include the use of tobacco and the effect of bacterial colonization of the mouth and stomach on nitrate metabolism. In addition, *Helicobacter pylori* eradication and increased gastrin levels are also proposed as risk factors. Dietary consumption of vitamin C, vitamin B6, folate, beta carotene, and fiber protect against esophageal adenocarcinoma. Long-term nonsteroidal anti-inflammatory use also has a protective effect.

Unlike adenocarcinoma of the esophagus, squamous cell carcinoma of the esophagus is associated with factors such as alcohol use, tobacco use, certain dietary habits that are localized to specific geographic areas, and certain viral infections. This type of cancer is prevalent in China, northern India, Iran, and certain parts of Africa. In terms of the location of the cancer, the adenocarcinoma is usually found in the lower two thirds of the esophagus, whereas squamous cell carcinoma is normally detected in the mid- and proximal esophagus.

G&H What is the incidence rate of Barrett esophagus progressing into cancer?

NB Several reports have attempted to address this issue. Prospective studies conducted in the United States and

Italy suggest that the incidence of Barrett esophagus progression to cancer is approximately 0.45% per year. These figures are based upon the studies performed on patients with 160–180 patient years of follow-up. Although the incidence rate is approximately 0.5% when all the numbers are analyzed together, the rate reportedly ranges from 0.4% to 2% per year. According to these figures, when looking at all Barrett esophagus patients (nondysplastic or dysplastic), a 55-year-old who has 30 years to live has a 15% lifelong risk of developing esophageal adenocarcinoma.

After stratifying the patient pool and focusing only on low-grade dysplasia, the risk will be anywhere between 5–10%. When examining only patients with high-grade dysplasia, the risk is quite substantial: reportedly 15–20% and up to 60% in some reports for patients undergoing surgery for high-grade dysplasia. According to the 2002 updated guidelines for the diagnosis, surveillance, and therapy of Barrett esophagus by Sampliner and the Practice Parameters Committee of the American College of Gastroenterology, a prospective cohort study of high-grade dysplasia patients who were followed for a period of 5 years was found to have a 25% 5-year risk for developing adenocarcinoma.

G&H Is surveillance/early detection still considered the main strategy for preventing the progression to cancer in these patients?

NB Early detection using screening is not a viable approach, as anywhere from 2% to 6% of the general population may have Barrett esophagus. This prevalence makes screening a very inefficient method of attempt-

ing to prevent cancer. However, if a patient is found to have Barrett esophagus, then surveillance does appear to be cost-effective. Several studies have examined this issue and noted that cost efficacy of surveillance is more favorable when considering surveillance of patients with dysplasia. Although somewhat controversial, high-grade dysplasia, which is almost synonymous with cancer, does require endoscopic or surgical intervention to achieve the goal of cancer prevention. Recent studies are suggesting that high-grade dysplasia or even early cancers can be managed with endoscopic therapy, with surgery being reserved mainly for the later stages of esophageal cancer.

G&H Could you discuss the data available thus far regarding potential chemopreventive agents as a strategy for preventing progression to esophageal cancer?

NB Chemoprevention in Barrett esophagus is still in the research phase and being undertaken by different institutions; it is not yet available in common clinical practice. There have been many studies of various chemopreventive agents, but all of them either involve preclinical in-vitro work, animals, or epidemiologic data. Epidemiologic data suggest that patients using nonsteroidal anti-inflammatory agents or proton pump inhibitors are at a lower risk of progression to cancer. There are preclinical studies using cell culture and animals showing that the use of anti-inflammatory agents, difluoromethylornithine, anti-oxidants from grapes and red wine, and intervention to reduce oxidative stress prevent carcinogenesis. Studies have also been conducted on statins; however, results were not impressive.

In terms of ongoing clinical trials, there are four important studies that hopefully will shed some light on chemoprevention: ASPECT, a UK-based trial on aspirin and esomeprazole; a cancer prevention networks trial that I am part of that is examining low- and high-dose aspirin with proton pump inhibitors; a trial on epigallocatechin gallate (EGCG), the green tea; and a clinical trial on the use of ursodeoxycholic acid. Most of these trials have sound epidemiologic or preclinical rationale. We recently looked at the combination of aspirin and ursodeoxycholic acid in a preclinical setting and found this strategy to be an effective approach for preventing cancer, and there is already discussion to make this a component of the cancer prevention networks trial application.

The only completed chemoprevention trial in Barrett esophagus relates to the use of celecoxib in patients with high-grade dysplasia. The recent reports of COX-2

inhibitor-related cardiac problems have dampened the enthusiasm in any of the coxibs. A survey of patients from Harvard and Massachusetts General Hospital in the *American Journal of Gastroenterology* last year asked patients if they would be willing to take agents to prevent cancer. The patients who had coronary artery disease were concerned and did not want to take any risks with coxibs; however, the majority of patients were comfortable taking aspirin for chemoprevention.

G&H Could you discuss the rationale behind the use of these chemopreventive agents?

NB There is good evidence that reflux and chronic injury are associated with the process of carcinogenesis and that more injury or more severe GERD has more serious complications, including dysplasia and cancer. Being overweight has also been associated with carcinogenesis. Studies have shown that proton pump inhibitors improve cell differentiation and downregulate the markers of cell proliferation in patients as well as in cell culture. Based upon these findings and associations, one can argue that interventions to prevent chronic injury could prevent carcinogenesis. Two epidemiologic studies, one from Australia and one from Arizona, have suggested that patients who take proton pump inhibitors are also at a lower risk of cancer. Together, these data provide the rationale to investigate whether the use of proton pump inhibitors alone or in combination with other agents will be a useful strategy. For instance, combining proton pump inhibitors with aspirin makes sense. Epidemiologic data of patients who have never taken aspirin versus patients who have taken aspirin within 6 months or patients who have been taking aspirin continuously show that the use of aspirin lowers the risk of developing adenocarcinoma. Proton pump inhibitors can decrease the side effects of aspirin, and aspirin can reduce the possibility of COX-2 activation that can result from hypergastrinemia due to proton pump inhibitor use. Using agents that have more than one indication (eg, cardioprotection, colorectal cancer prevention, along with prevention of esophageal adenocarcinoma) is a good rationale for using an agent for chemoprevention.

There is also a good deal of interest in how different dietary supplements or dietary modifications may have an impact (eg, a diet rich in vitamins and fruits versus a regular diet; a low-carbohydrate diet versus any type of diet; and various approaches to change the body mass index). Berries, green tea, and related agents that scavenge free radicals are currently being tested in the preclinical setting and may show up in clinical research areas.

G&H In which specific patient groups has chemoprevention of Barrett esophagus been studied?

NB Most of the studies mentioned above have used chemoprevention in nondysplastic Barrett patients or low-grade dysplasia patients. The risk of progression into cancer in these patients is low, which means that a large number of patients is needed in a study that may last for almost a decade to really see a cancer risk reduction.

High-grade dysplasia patients or patients with very early cancers have already reached a stage where agents alone may not be safe or effective to be ethically administered as first-line therapy. Thus, chemopreventive agents can piggyback with endoscopic mucosal resection or a type of ablation.

Patients who are already diagnosed with high-grade dysplasia or cancer and have undergone either endoscopic ablation or surgical resection comprise another patient group of interest. In these patients, chemoprevention may be able to prevent the recurrence of Barrett esophagus or development of dysplasia.

G&H Are there any risks or disadvantages to using chemopreventive strategies?

NB The risk/benefit ratio should be considered for any approach that is undertaken. For example, in a healthy patient with high-grade dysplasia or more advanced disease, offering a therapy that is very safe but not that effective would be inefficient. Unless the agent is very effective, using these agents would not make a difference and would actually place patients at risk for developing cancer that would have been otherwise managed endoscopically or surgically. Using a strategy may backfire if the drug has more side effects than benefits. Using such an agent would not only be riskier, it would likely not serve any purpose to the patient. One should decide whether or not to use an agent based upon the disease stage, patient's health status, and safety of the agent. If the agent is very safe (safe enough that it could practically be put in the city water supply) and is inexpensive and the patient has no dysplasia, that would be a reasonable strategy.

On the other hand, tolerance to risk may increase if the agent is very effective and the patient does not have any other management options. If the patients are quite advanced in their disease but do not have options because

of their age or comorbidities that put them at high risk, it is reasonable to use agents that carry a high risk of complications but are otherwise effective. This is where the preclinical studies come into play. Based upon our prior knowledge of how safe and effective agents are, they may be used as adjunctive therapy. For example, at present, some studies using aspirin are also using proton pump inhibitors, the combination of which has been shown to decrease the risk of bleeding. Similarly, EGCG and ursodeoxycholic acid appear to be safe in studies because these agents do not pose much risk.

Finally, it is important not to overtreat patients with Barrett esophagus. The risk of cancer in some patients may be overestimated, and patients may sometimes be managed in ways that do not serve them or their payers well. For instance, starting treatment in a patient whose risk of cancer is very low is not reasonable, though it is often done when the patient is very concerned. Also, if a patient is, say, already 85 years old and has nondysplastic Barrett esophagus, surveying this patient who has not developed cancer while having Barrett for 20 years does not make sense, as no procedures are without risk. There can be medication-related complications or endoscopy-related perforations or other complications. Similarly, performing ablation without a clear understanding of the risks and benefits to eliminate Barrett esophagus also appears to be premature, and it is not necessary to obtain irregular Z-line biopsies to detect Barrett esophagus if there is no endoscopic evidence of Barrett esophagus.

Suggested Reading

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