INTRODUCTION

Chemoprevention refers to the practice of using chemical compounds to prevent, slow down or reverse the development of cancer. Recent data suggest a role for chemopreventive medications in reducing the risk of colorectal carcinoma (CRC) in patients with chronic inflammatory bowel disease (IBD). Strategies to reduce or prevent the complications associated with invasive cancer are essential in this high-risk population. Efforts in the past have focused largely on secondary prevention of cancer through the use of surveillance colonoscopy, with subsequent colectomy for patients in whom dysplasia or cancer is found. This approach has several shortcomings, however. There have been no prospective trials evaluating the success of this approach to prevention. Colonoscopy is not sufficiently sensitive in identifying some pre-malignant areas of dysplasia which may arise from flat mucosal lesions in patients with colitis that are either not visible to the endoscopist with existing standard technologies or are simply missed given the large surface area of colonic epithelium. Even when dysplastic lesions are successfully identified by colonoscopy, no proven therapy exists for regression of these lesions. As dysplastic lesions may be associated with concomitant or subsequent colorectal cancer, surgical removal of the colon is therefore recommended, with the strength of that recommendation varying based on the degree of dysplasia and available prevention evidence (1). Given the limitations of colonoscopic surveillance, recent prevention strategies have focused on the possibility of primary prevention, highlighting a possible role for chemopreventive medications. Candidate medications for chemoprevention of cancer in IBD include 5-aminosalicylates (5-ASA), folate, ursodeoxycholic acid, azathioprine and 6-mercaptopurine. This article will review and summarize the available evidence regarding chemoprevention of colorectal cancer in patients with IBD.
RISK OF COLORECTAL CARCINOMA IN IBD

Patients with IBD have an established increased risk of developing colorectal cancer. While this association is well established for patients with ulcerative colitis (UC) (2), more recent data suggest this increased risk also applies to patients with Crohn’s disease (CD) involving the colon (3,4). Both referral-based and population-based studies support this increased risk. Several risk factors for dysplasia and CRC have been identified in this patient population, including: longer duration of disease (2), greater extent of disease (5), younger age at diagnosis (independent of duration of disease)(5), a family history of CRC (independent of a family history of IBD) (6,7), coexistent primary sclerosing cholangitis (PSC) (8), possibly backwash ileitis (9), and, more recently, the degree of histologic inflammation of the colon (10). Apart from the degree of inflammation, these risk factors are immutable, reinforcing a role for chemoprevention in mitigating cancer risk in this patient population.

A meta-analysis performed by Eaden, et al quantified the cumulative risk of cancer in patients with chronic ulcerative colitis with regard to disease duration (2). In their review of 114 studies, 41 of which met inclusion criteria, they demonstrated a 2% risk of cancer after 10 years of chronic UC, 8% risk after 20 years, and 18% risk after 30 years. More recently, however, Rutter, et al reported on their 30-year experience at the St. Mark’s Hospital in London describing a cumulative incidence less than that in the meta-analysis (11). Chronic Crohn’s colitis has also been associated with increased risk of dysplasia or cancer in a number of population-based studies, although the relative risk varies from 0.9 to 3.4 (12,13). This wide variation in the reported relative risk is partially explained by inclusion of some Crohn’s patients without colonic involvement. Although only one percent of all cases of CRC occur in patients with IBD (14), CRC accounts for approximately one sixth of all deaths in IBD patients (15), making it a major source of morbidity and mortality in IBD, and underscoring the importance of developing an effective prevention strategy in this high-risk population. As a cornerstone of this preventive strategy, the potential for successful chemoprevention offers an opportunity to reduce mortality and morbidity by intervening early enough to avoid colectomy in addition to preventing invasive cancer.

THE ASSOCIATION BETWEEN DYSPLASIA AND ADENOCARCINOMA IN IBD

Colorectal carcinoma that develops in the setting of IBD has a unique pathogenesis that differs from the carcinogenic sequence of sporadic CRC. When cancer develops in IBD, it appears to develop from dysplasia in flat mucosa rather than from adenomatous polyps, and it is often multifocal (16). Additionally, the progression from normal mucosa to dysplasia to frank carcinoma occurs much more quickly or in a non-linear fashion when compared to sporadic CRC (16). Low-grade dysplasia is associated with a subsequent high-grade dysplasia or cancer in 29%–54% of patients over five years, and is associated with a coexistent cancer at the time of dysplasia diagnosis in approximately 19% of cases (1,11). Furthermore, high-grade dysplasia has been found to be associated with co-existing cancer in as many as 45% of colectomy specimens (1,11). This presents several challenges for detection of premalignant lesions during colonoscopic examination. Flat lesions are more difficult to visualize at the time of colonoscopy, and the multifocal nature of dysplasia in IBD has led to practice guidelines that require numerous random biopsies throughout the involved mucosa. Unfortunately, interpretation of these biopsies is limited by ascertainment and by pathological review. Truly successful chemoprevention could improve dysplasia detection by reducing the need for such a cumbersome and limited approach to detection.

RATIONALE AND GOALS OF CHEMOPREVENTION

Given the limitations of current cancer prevention strategies in IBD it is imperative to explore alternative approaches to prevention. Chemoprevention represents an exciting and promising approach by offering the hope of intervening early in the carcinogenic sequence, prior to the development of dysplasia or carcinoma, thereby obviating the need for colectomy. While the ideal chemopreventive medication would completely eliminate CRC risk, such an expectation is unrealistic at present. Rather, the goal for chemoprevention should be to minimize CRC risk, allowing for a reduction in the number of patients requiring surgery for dysplasia, and a decrease in the number of cases of invasive cancer. Another reasonable goal would be to prolong the interval between colonoscopic screening examinations.
The ideal chemopreventive agent should also have a well-understood mechanism of action, be safe, effective, affordable and acceptable to patients (Table 1). Among the agents commonly used in the management of ulcerative colitis, several candidate medications have been proposed for potential chemoprevention, including 5-ASA compounds, folate, ursodeoxycholic acid (UDCA), corticosteroids and immunomodulators such as azathioprine and 6-mercaptopurine.

**Evidence for 5-ASA as a Chemopreventive Agent**

Several studies have described a role for 5-ASA in chemoprevention. This data comes from case-control, cohort and population-based studies. Unfortunately, no prospective data in humans exist, owing to the prohibitively large numbers of patients and time required to conduct a sufficiently powered study, as well as the ethical constraints of withholding 5-ASA medications (a mainstay of therapy for IBD) from the control group (17). Nevertheless, sound evidence from observational studies and theoretical rationale from basic science literature support the use of 5-ASA medications for chemoprevention (18).

Several mechanisms have been proposed for 5-ASA interrupting the sequence of progression from dysplasia to carcinoma in IBD patients. First, 5-ASA is a derivative of aspirin, which has been shown to decrease the risk for cancer in non-IBD patients with polyps (19). Additionally, 5-ASA inhibits cell proliferation, induces apoptosis, and may further act as a potent scavenger of free radicals, thereby enhancing DNA repair (20–23). Furthermore, 5-ASA may exert a chemoprotective effect simply by controlling inflammation, although this mechanism remains unproven.

Several studies have been published in the past decade examining the effect of 5-ASA on colon cancer risk in IBD. These studies have yielded mixed results with regard to the potential protective effect of 5-ASA medications. Strong data in support of 5-ASA for chemoprevention comes from a case control study performed by Eaden, et al in the United Kingdom, in which 102 patients with chronic UC and colorectal cancer were identified and matched to 102 patients with UC who did not develop neoplasia (6). Cases and controls were matched based on age, sex, duration and extent of disease. In this study, use of aminosalicylates at doses of 1.2 g/d or greater was associated with a 75% reduction in the risk of cancer. In addition, regular visits to the doctor, steroids and colonoscopies were associated with a lower risk of cancer.

Our subsequent study at the University of Chicago matched 26 patients with dysplasia or CRC to 96 controls based on extent of disease, duration of disease, and age of diagnosis. Additional variables such as family history of colorectal cancer, smoking history, folic acid use, and PSC were examined as well. Results showed that patients with dysplasia or CRC were more likely to have a family history of CRC than those without neoplasia, and multivariate regression showed a 72% risk reduction for use of aminosalicylates at a dose of at least 1.2 g/d (AOR 0.28, 95% CI 0.09 to 0.85) (24). In this study a dose-response relationship was observed, such that the risk of dysplasia or cancer was inversely related to the total dose of 5-ASA. A recent case control study by Velayos, et al described an odds ratio of 0.4 (0.2–0.9) for the development of cancer among patients taking 5-ASA, however this protective effect was no longer significant after five years (25). Other studies have also identified a protective effect from regular use of 5-aminosalicylates (26–28).

Not all of the published data shows a benefit from taking 5-ASA, however. Bernstein, et al conducted a population-based study in Canada that failed to show a protective effect of 5-ASA (29). Using the Manitoba IBD Epidemiology Database, they identified 25 cases of IBD with CRC and matched them to 348 controls with IBD who did not develop CRC. The results showed a non-significant trend toward higher likelihood of 5-ASA medications in the cancer group.

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A meta-analysis of 5-ASA use and the risk of dysplasia or cancer was performed by Velayos, et al that included nine case control and cohort studies, enrolling a total of 1,932 patients, including 334 cases of CRC and 140 cases of dysplasia. Results of their analysis revealed a pooled odds ratio of 0.51 (0.38–0.69) for the development of dysplasia or cancer among patients with IBD who used regular 5-ASA drugs (30). Given the substantial heterogeneity of results from individual studies, this pooled data represents our current attempt to estimate the protective effect of 5-aminosalicylates.

**EVIDENCE FOR FOLATE AS A CHEMOPREVENTIVE AGENT**

Folate has been shown to be protective against the development of several cancers, including sporadic CRC. This finding, coupled with the observation that many IBD patients may be folate-deficient, has spawned interest in examining folate as a potential chemopreventive agent in IBD. In 1997, Lashner, et al looked at a cohort of 98 patients who had colitis extending beyond the splenic flexure for at least eight years, and analyzed the risk of dysplasia or cancer with respect to folate use over the prior six months (31). Although the results were not statistically significant, there was a trend toward a protective effect for folate. Additionally, the authors demonstrated a non-significant dose-response relationship in which the relative risk for dysplasia in patients taking 1 mg of folic acid and 0.4 mg of folic acid were 0.54 (0.20–1.48) and 0.76 (0.36–1.61), respectively.

In a study by Rutter, et al designed to examine potential risk factors for neoplasia in patients with longstanding UC, the authors found a numerical but non-significant protective effect amongst the patients taking folate (OR 0.40, 95% CI 0.05–3.42) (10). However, this study contained only a small number of patients taking folate.

**EVIDENCE FOR URSODEOXYCHOLIC ACID AS A CHEMOPREVENTIVE AGENT**

Ursodeoxycholic acid (UDCA), a synthetic bile acid, has been studied in patients with PSC and UC. In a prospective randomized, placebo-controlled trial by Pardi and colleagues at the Mayo Clinic, 52 patients with chronic PSC and chronic UC (mean 13 years) were followed for a total of 355 person years (32). Patients randomized to receive UDCA had a relative risk of 0.26 (95% CI 0.60–0.92) for the development of dysplasia or CRC compared to placebo. Likewise, a study by Tung and colleagues at the University of Washington followed 59 patients with UC and PSC and found a strong negative association between UDCA use and the development of dysplasia, with an odds ratio of 0.18 (p = 0.005) (33). Generalizability of these results is hampered, however, by the fact that patients who took UDCA in this study were older at diagnosis and had a shorter duration of disease than controls. Also, this study has been critiqued because the cancer rate in the control population was much higher than in similar studies. In a case-control study by Wolf, et al looking at PSC patients with UC, there was a nonsignificant trend toward lower risk of dysplasia or cancer in patients who took UDCA and a significant decrease in all-cause mortality (34). Given these findings it is reasonable to advocate UDCA for chemoprevention of CRC in this unique patient population. The role of UDCA in patients with UC but without PSC remains unclear.

**EVIDENCE FOR OTHER ANTI-INFLAMMATORY DRUGS AS CHEMOPREVENTIVE AGENTS**

Since one of the proposed mechanisms of 5-ASA medications in chemoprevention is their anti-inflammatory effect, it is reasonable to consider whether other anti-inflammatory medications might also have a protective effect. Non-steroidal anti-inflammatory drugs (NSAIDs), for example, have been shown to cause polyp regression in sporadic or familial CRC. However, cancer in IBD has distinct molecular alterations that distinguish it from sporadic or familial CRC, and caution should be taken in extrapolating the results of studies from these other populations. A case control study performed at a Veterans Administration population compared patients with IBD and a comorbid illness requiring chronic NSAID use to patients with IBD who did not require chronic NSAID use (35). The data showed a non-significant trend toward reduced risk of CRC amongst patients taking NSAIDs, but the
lack of information regarding duration and extent of disease make it difficult to interpret these results critically. Velayos, et al performed a study in which 188 cases of CRC in patients with UC were matched to 188 controls with UC. The results of multivariate analysis revealed a protective effect for NSAIDs (OR 0.1; 95% CI: 0.03–0.5) (25). Clinical application of this data is limited, however, by the fact that NSAIDs are typically avoided in patients with IBD as they can cause symptomatic relapses.

The data regarding corticosteroids for chemoprevention is mixed. While some authors have described a protective effect of systemic steroids (6,25), the adverse side effect profile of these medications precludes their long-term use as chemopreventive agents.

### EVIDENCE FOR PURINE ANALOGS AS CHEMOPREVENTIVE AGENTS

Azathioprine and 6-mercaptopurine (6-MP) have become commonly used medications for maintenance of steroid-free remission in both ulcerative colitis and Crohn’s disease. Interest in exploring the potential chemoprotective effects of these medications has been tempered by concerns arising from the renal transplant literature that they may increase risk of certain malignancies such as basal cell carcinoma or lymphoma. Fraser, et al investigated the effect of azathioprine on cancer risk in patients with IBD with a retrospective chart review and found no significant difference in rates of neoplasm (CRC, lymphoma, skin cancer, or other tumors) associated with azathioprine use (36). Likewise, a study by Matula and colleagues found no effect of 6-MP or azathioprine on the rate of progression to advanced neoplasia or any neoplasia in 315 patients with UC who were followed for an average of eight years (37). At this time there is no convincing evidence to suggest a chemoprotective effect of these medications, but the absence of evidence to suggest carcinogenesis of these commonly used medications is reassuring.

### CONCLUSIONS

Patients with IBD have a high-risk of developing colorectal cancer, and given the chronic nature of these diseases, there is an obvious role for effective chemoprevention in minimizing this risk. Ideally, chemoprevention should be viewed as a supplement to colonoscopic surveillance, and as the cornerstone of a comprehensive prevention strategy. The strongest evidence for chemoprevention exists for ursodeoxycholic acid in patients with PSC and UC, and this agent should be offered routinely to these patients. Although the existing data is mixed, there is good rationale to consider aminosalicylates as potential chemopreventive agents in chronic UC and we advocate an informed discussion with patients about this possibility and to encourage adherence to the prescribed medical regimen. Folate has a good rationale and excellent safety profile, but insufficient evidence of its chemoprevention.
At this time, there are insufficient data to recommend long-term chemopreventive agents in chronic colitis. The adverse side effect profile of corticosteroids and NSAIDs precludes their use as protective benefit. The more frequent and longer-term use of these therapies will allow for additional studies in the future (Table 2).

References

17. Rubin DT, Lashner BA. Will a 5-ASA a day keep the cancer (and dysplasia) away? Am J Gastroenterol, 2005;100:1354-1356.