The Potential for Medical Therapy to Reduce the Risk of Colorectal Cancer and Optimize Surveillance in Inflammatory Bowel Disease

Christopher G. Chapman, MD, David T. Rubin, MD*

KEYWORDS

- Medical therapy • Colorectal cancer • Inflammatory bowel disease
- Surveillance endoscopy

KEY POINTS

- Medical therapy, as in the case of 5-aminosalicylic acid, may have mechanistic plausibility for direct antineoplastic properties, but others, such as thiopurines, do not, suggesting that there is a primary chemopreventive benefit derived from the ability to achieve endoscopic and histologic healing.
- Mucosal healing induced by medical therapy may also provide a secondary preventive benefit by allowing improved endoscopic and histologic detection and differentiation between reactive epithelial changes and dysplasia.
- Of the many risk factors for the development of colitis-associated colorectal cancer (CRC), one of the most modifiable for a treating physician is the presence and severity of chronic inflammation.
- Although the mechanism of the declining risk of CRC in IBD is unclear, the likely determinants are a combination of primary prevention resulting from improved medical therapies able to induce mucosal healing, and secondary prevention derived from improved surveillance endoscopy technologies.

INTRODUCTION

Current goals of therapy for inflammatory bowel disease (IBD) are the induction and maintenance of inflammatory symptoms to provide an improved quality of life, to reduce the need for long-term corticosteroids, and to reduce other long-term outcomes such as disability, hospitalization, and colorectal cancer (CRC).[1] Although the success of this latter goal has been difficult to measure, the overall risk of

Inflammatory Bowel Disease Center, University of Chicago Medicine, 5841 South Maryland Avenue, MC 4076, Chicago, IL 60637, USA
* Corresponding author.
E-mail address: drubin@medicine.bsd.uchicago.edu

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IBD-associated colorectal cancer (CRC) appears to have declined over the past 30 years.[2] The observed decrease in CRC is thought to be due to a combination of factors, including improvements in the ability to identify and to quantify patients at risk and to detect precancerous lesions, and the direct and indirect reduction in cancer resulting from effective medical and surgical therapies of the underlying inflammation.

Some of the well-defined genetic molecular pathways leading to sporadic or hereditary CRC also appear to be present in colitis-associated CRC. However, IBD-associated adenocarcinoma does not seem to follow the discrete adenoma-to-CRC sequence of events.[3] Rather, a progression, from inflamed mucosa to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to invasive adenocarcinoma, in IBD remains presumed and unproven. In fact, neoplasia in colitis takes different forms, a fact that has resulted in difficulty classifying, identifying, and developing appropriate prevention strategies for it. Cells from colonic mucosa in patients with chronic colitis have the molecular fingerprints of dysplasia and cancer, including genomic instability (aneuploidy), aberrant DNA methylation, and p53 mutations, even before there is any histologic evidence of dysplasia or cancer.[4] It is thought that such a "field effect" of CRC risk is induced by chronic long-standing mucosal inflammation.

Most recently, the degree of inflammation has been shown to be a significant risk factor for neoplasia in IBD.[5,6] In addition to the presence and degree of severity of active endoscopic/histologic colonic inflammation, additional established IBD-associated dysplasia and CRC risk factors include extent and duration of disease, family history of CRC, concomitant primary sclerosing cholangitis (PSC), young age at diagnosis, and presence of postinflammatory polyps and strictures.[4,6] Of these risks, the only modifiable risk factor may be the degree of active inflammation. Therefore, it has been proposed that effective disease control through abrogation of inflammation may also reduce CRC risk in the individual patient.

Although the culmination of this evidence to date supports the clinician-adopted theory that treating to achieve mucosal healing will reduce the risk of CRC in patients with IBD, it remains uncertain how these recommendations can be practically applied by clinicians trying to develop effective dysplasia and CRC prevention strategies in IBD. This article summarizes the potential for medical therapy to reduce the risk of CRC via primary and secondary prevention, and offers practical ways in which a goal of mucosal improvement or healing may be incorporated into clinical practice (**Box 1**).

DEFINITION OF REMISSION IN IBD: AN EVOLVING TARGET

The end point of escalation of therapy in IBD has traditionally been based on adequate symptom control.[7] Despite patient satisfaction in the achievement of clinical

Box 1
Mechanisms by which medical therapy may reduce colorectal cancer in IBD

Primary chemoprevention

- Medical therapy reduces inflammation over time
- Medical therapy has unique chemoprotection mechanisms

Secondary prevention

- Treatment to achieve a healed bowel results in more accurate neoplasia detection by endoscopy
- Reduction in histologic inflammation improves pathologist's diagnosis of neoplasia