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TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment

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Abstract

In patients with inflammatory bowel disease (IBD), chronic inflammation is a major risk factor for the development of gastrointestinal malignancies. The pathogenesis of colitis-associated cancer is distinct from sporadic colorectal carcinoma and the critical molecular mechanisms underlying this process have yet to be elucidated. Patients with IBD have also been shown to be at increased risk of developing extra-intestinal malignancies. Medical therapies that diminish the mucosal inflammatory response represent the foundation of treatment in IBD, and recent evidence supports their introduction earlier in the disease course. However, therapies that alter the immune system, often used for long durations, may also promote carcinogenesis. As the population of patients with IBD grows older, with longer duration of chronic inflammation and longer exposure to immunosuppression, there is an increasing risk of cancer development. Many of these patients will require cancer treatment, including chemotherapy, radiation, hormonal therapy, and surgery. Many patients will require further treatment for their IBD. This review seeks to explore the characteristics and risks of cancer in patients with IBD, and to evaluate the limited data on patients with IBD and cancer, including management of IBD after a diagnosis of cancer, the effects of cancer treatment on IBD, and the effect of IBD and medications for IBD on cancer outcomes.

Key words: Inflammatory bowel disease; Cancer; Anti-tumor necrosis factor; Immunosuppression; Chemotherapy; Radiation

Core tip: Patients with inflammatory bowel disease (IBD) and cancer represent a challenging population. Gastroenterologists and oncologists caring for patients with IBD and cancer are increasingly confronted with questions regarding the management of IBD after a diagnosis of cancer, and conversely, the management of cancer in patients with IBD. This review seeks to explore the characteristics, risks, and pathogenesis of cancer in patients with IBD, and to evaluate the data on patients with IBD and cancer, including the interaction between IBD and cancer treatment.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract. Although the disease pathogenesis is not fully understood, inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors. Together, IBD is estimated to affect more than 0.4% of Europeans and North Americans, a number that is expected to increase over time[1]. It is well recognized that patients with IBD are at an increased risk of developing colorectal cancer (CRC), primarily the result of chronic intestinal inflammation[2-4]. More recently, patients with IBD have also been shown to be at increased risk of developing extra-intestinal malignancies, thought to be a consequence of immunosuppressive therapies and an underlying inflammatory state[5].

As the population of patients with IBD grows and ages, there is an inevitable increase in the risk of cancer development. Moreover, many of these patients may require cancer treatment, including chemotherapy, radiation, and immunotherapy, and many may require further treatment for their IBD. The focus of this review is to evaluate the characteristics, pathogenesis, and risks of cancer in patients with IBD, and to explore the relationship between IBD and cancer treatment.

IBD AND RISK OF CANCER

Cancer secondary to chronic intestinal inflammation

In patients with IBD, chronic intestinal inflammation is the primary risk factor for the development of gastrointestinal malignancy. Cancers as a result of chronic intestinal inflammation include CRC, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and cholangiocarcinoma (Table 1)[6].

Table 1 Cancer secondary to chronic intestinal inflammation

Cancer type	Standardized incidence ratio
Colorectal cancer[3]	5.7 (95%CI: 4.6-7.0)
Small bowel adenocarcinoma[20]	27.1 (95%CI: 14.9-49.2)
Intestinal lymphoma[36]	17.51 (95%CI: 6.43-38.11)
Anal cancer[60]	Data not available
Cholangiocarcinoma[23]	916.63 (95%CI: 297.88-2140.99) in UC

UC: Ulcerative colitis.

The risk and pathogenesis of inflammation-associated cancer has chiefly been described in colitis-associated CRC. In a meta analysis, quantitative estimates of CRC risk in UC have been reported to be 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease[3]. Moreover, studies of CRC in UC have noted a high concordance between CRC risk with the location and extent of disease, with a standardized incidence ratio (SIR) of 1.7 for proctitis, 2.8 for left-sided colitis, and 14.8 for pancolitis[7]. All of these studies support the strong association between inflammation and cancer development.

Patients with IBD develop colon cancer in a manner similar to well described sporadic molecular mechanisms including mutations in the adenomatous polyposis coli (*APC*) gene, aneuploidy, DNA methylation, microsatellite instability (MSI), activation of the oncogene *k-ras*, activation of *COX-2*, and mutation in tumor suppressor genes *DCC/DPC4*, and eventual loss of *p53* function[8]. However, underlying colonic inflammation changes the timing and sequence of these genomic changes, yielding a process of carcinogenesis that is faster and multifocal[4]. Contrary to sporadic cancers in which the dysplastic precursor is the adenomatous polyp, dysplasia in patients with IBD can be localized, diffuse, or multifocal[4,9].

Studies mapping genomic instability secondary to DNA aneuploidy in patients with IBD indicate that these cell populations became more widely distributed, occupying larger areas of colonic mucosa[9]. Over time, further subpopulations with increasingly unstable genomics arise and expand, representing a whole field change, marking the entire colon at risk for further carcinogenesis[9,10].

In terms of specific molecular mechanisms that differ between colitis-associated cancer and sporadic cancer, early mutation in p53 is thought to play a fundamental role. Changes in p53 have been found in up to 85% of colitis-associated cancers[11]. Furthermore, alterations in p53 have been observed in biopsies from inflamed mucosa in more than 50% of patients with UC who did not have cancer, indicating a significant role of inflammation in these mutations[12]. In addition, loss of APC, an early event in the development of

Table 2 Cancer secondary to immunosuppression

Increased risk under anti-metabolites	Increased risk under anti-TNFα	Increased risk under anti-metabolite with anti-TNFα
Non-Hodgkin lymphoma[33-35]	Melanoma[42]	Hepatosplenic T-cell lymphoma[38]
Acute myeloid leukemia and Myelodysplastic syndromes[61]		
Non-melanoma skin cancers (basal and squamous cell carcinomas)[39-41]		
Urinary tract cancers[62]		

TNF-α: Tumor necrosis factor alpha.

sporadic CRC, is less frequent and tends to occur later in colitis-associated cancer[13]. DNA methylation also differs with increased hypermethylation of several genes, including *hMLH1* and *p16*, occurring earlier and contributing to microsatellite instability[14].

The immune response and oxidative stress play a critical role in the initiation and progression of carcinogenesis, contributing to the aforementioned molecular mechanisms leading to cancer. The inflammatory microenvironment of IBD, consisting of a variety of immune cells, epithelial cells, stromal cells, cytokines, and chemokines, has many similarities to the microenvironment of cancers, suggesting similar inflammatory mediators and mechanisms that promote both IBD and cancer development[15]. These mediators, produced by inflammatory cells, include tumor necrosis factor alpha (TNF-α), ILs-1, 6, 12, 13, 17, 22, and 23[15]. The interaction between the signaling of these cytokines and immune response play a major role in inflammation and colitis-associated cancer.

The increased expression of several inflammation-associated genes in IBD, such as cyclooxygenase-2 (COX-2) and nitric oxide synthase-2 (NOS-2), have also been noted in colonic neoplasia[12]. It is thought that reactive oxygen and nitrogen species produced by inflammatory cells expressing these genes not only directly damage colonic epithelium, but also contribute to the genetic alterations driving carcinogenesis[9].

In addition, alterations in the microbiota contribute to colitis-associated cancer. In mouse models of colitis-associated cancer susceptible to inflammation or cancer, cancer did not develop when the mice were germ-free or treated with antibiotics[16,17]. Studies of the microbiota in patients with CRC have demonstrated varying populations of bacteria that differ from cancer-free controls, suggesting that the complex interaction between the host genome, colonic epithelial-cell receptors, and the luminal microbiota create an environment conducive to carcinogenesis. Stool samples derived from CRC patients had higher levels of *Fusobacterium*, *Enterococcus*, *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus*, and *Peptostreptococcus*, *Firmicutes*, *Bacteroidetes*, and a depletion of bacteria belonging to *Lachnospiraceae* family compared to controls[18,19]. Although we are just beginning to understand the association between specific gastrointestinal microbes and cancer, much remains unknown regarding the causes and effects of these relationships and how manipulating the microbiome may have therapeutic potential.

In addition to CRC, small-bowel adenocarcinoma, specifically ileal carcinoma, has been shown to be significantly associated with the severity and duration of CD, and it is 20 to 30 fold more common in patients with CD compared to the general population[20]. Moreover, it is often found in areas with previous or synchronous ileal dysplasia, suggesting that it may evolve in a similar manner to the molecular and immune mechanisms of CRC described above[21]. In addition, cholangiocarcinoma, when associated with UC-primary sclerosing cholangitis (PSC), yields a risk nearly 160 fold greater than controls, suggesting the inflammatory state of IBD-PSC may contribute to biliary carcinogenesis[22,23].

Cancer secondary to immunosuppression

Given that chronic inflammation underlies the disease state of IBD, medications that mitigate inflammation by suppression of the immune system represent the cornerstone of treatment. In addition to treating IBD, it is postulated that these medications, such as immunomodulators [thiopurines (azathioprine or mercaptopurine) or methotrexate] and biologic agents (TNF-α antagonists), may reduce the incidence of inflammation-associated cancer. However, given that immunomodulators and biologic agents act on the immune system, they may also promote carcinogenesis.

Thiopurines and methotrexate promote the development of cancer by a variety of mechanisms including direct alteration in DNA, activation of oncogenes, reduction in physiologic immunosurveillance of malignant cells, and impaired immune control of oncogenic viruses[24-26]. Less is known about the carcinogenic potential of biologic therapies that block TNF-α and existing molecular data is inconsistent. TNF-α has been shown to exhibit anti-tumor effects by initiating cellular apoptosis of malignant cells, but it is secreted by most tumors to facilitate cellular survival and enhance neoplastic proliferation as a pro-tumor inflammatory cytokine[27-29].

Several studies have indicated a risk of therapy-associated malignancies in IBD patients. Population-based cohort and meta-analyses have demonstrated that current use of thiopurines for IBD is associated with a 1.3 to 1.7 overall relative risk of cancer, which is reversible after withdrawal[30,31]. Current exposure to TNF-α antagonists has not been shown to be associated with an overall excess risk of cancer, but data is very limited[32]. Specific cancers thought secondary to long-standing immunosuppression in the setting of IBD include lymphomas, acute myeloid leukemia, myelodysplastic syndromes, skin cancers, and urinary tract cancers (Table 2).

For lymphoma, multiple studies have demonstrated incidence ratios of non-Hodgkin lymphoma following thiopurine exposure ranging from 1.6 to 37.5, with no excess risk attributed to IBD itself[33-35]. The exception to this is primary intestinal lymphoma, where duration and severity of CD play a primary role[36]. In the setting of thiopurines, most lymphoma is Epstein-Barr virus (EBV)-associated and thought to result from the loss of immune control of EBV-infected B lymphocytes[37]. Furthermore, there have been several cases of fatal early postmononucleosis lymphoma in young men who are previously seronegative for EBV[33]. In addition, Hepatosplenic T-cell Lymphoma, though very rare, is primarily associated with thiopurine exposure in combination with TNF-α antagonists in both adolescent and young males[38]. However, recent data suggests that there is no excess risk of lymphoma in patients with IBD exposed to TNF-α antagonists[32].

In a study from the Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France (CESAME) cohort, the risk of myeloid disorders was not increased among patients with IBD or ongoing thiopurine treatment (SIR = 1.54, 95%CI: 0.05-8.54), but patients with past exposures to thiopurines had an increased risk of myeloid disorders (SIR = 6.98; 95%CI: 1.44-20.36)[31].

For skin cancers, there is substantial evidence that thiopurines increase the risk of basal cell and squamous cell carcinomas, collectively known as nonmelanoma skin cancers (NMSC)[39-41]. In another study from the CESAME group, an increased risk of NMSC was observed in the patients with IBD and associated with ongoing thiopurine exposure (HR = 5.9; 95%CI: 2.1-16.4) and past thiopurine exposure (HR = 3.9; 95%CI: 1.3-12.1)[41]. However, in a large retrospective cohort of patients with IBD, there was no excess risk of nonmelanoma skin cancer attributable to TNF-α antagonists[40]. In addition, studies have demonstrated an increased risk of melanoma in patients with IBD, with no increased risk associated with thiopurine exposure[40-42]. Conversely, patients exposed to TNF-α antagonists have been found to be 1.5 to 2 times more likely to develop melanoma to patients with IBD who were not exposed to TNF-α antagonists[32]. As such, thiopurines increase the risk of NMSC whereas TNF-α antagonists increase the risk of melanoma.

Secondary or recurrent cancer in patients with a history of cancer

Given the above-mentioned risks of immunomodulator and biologic-associated malignancy, patients with a history of cancer were excluded from clinical trials of TNF-α antagonists. Additionally, there is substantial data within the transplant literature indicating that immunosuppression, such as thiopurines and calcineurin inhibitors, increases the risk of new and recurrent malignancies in patients with a history of cancer[43,44]. As such, oncologists and gastroenterologists generally suspend immunosuppression for IBD after a diagnosis of cancer, both while undergoing cancer treatment and during remission from cancer. This approach may worsen IBD and even complicate appropriate cancer management. Although there is little data on patients with IBD and a history of cancer, there is emerging data regarding the management of IBD after a diagnosis of cancer.

In 17047 patients in the CESAME prospective observational cohort, exposure to immunosuppression was independently associated with the development of cancer with an adjusted HR of 1.9 (95%CI: 1.2-3.0)[31]. However, it did not increase the risk of new or recurrent cancer in patients with a history of cancer[31]. Given the limited number of patients with IBD and a history of cancer with subsequent exposure to immunosuppression in the cohort, this conclusion only applied to thiopurine exposure and no conclusions were drawn on anti-TNF-α therapies[31].

A similar study from the New York Crohn's and Colitis Organization (NYCCO) representing a consortium of 8 academic medical centers found that nearly 30% of patients with IBD and a history of cancer developed new or recurrent cancer[45]. However, exposure to TNF-α antagonists, antimetabolites, or the combination was not associated with an increased risk of new or recurrent cancer within 5 years following a diagnosis of cancer (Log-rank P = 0.14)[45]. Furthermore, after adjusting for the risk of recurrence of prior cancer, there was still no difference in risk of new or recurrent cancer between exposure groups (anti-TNF-α HR = 0.32, 95%CI: 0.09-1.09; anti-TNF-α with an antimetabolite HR = 0.64, 95%CI: 0.26-1.59; antimetabolite HR = 1.08, 95%CI: 0.54-2.15)[45].

In addition, data from NYCCO showed that duration of anti-TNF-α after a diagnosis of cancer was not associated with the risk or type of new or recurrent cancer[45]. Studies within the rheumatoid arthritis literature corroborate these findings with data demonstrating no difference in the development of new or recurrent cancer in patients with a history of cancer who were subsequently exposed to anti-TNF-α agents compared with those receiving disease-modifying anti-rheumatic drugs alone[46,47]. However, given small sample sizes, these studies often grouped different types of cancers together. In the NYCCO study for example, all solid malignancies, such as breast, prostate, and lung, were grouped together. This statistical approach may not reflect the natural biologic activity of carcinogenesis and the direct effects of immunosuppression on cancer development, limiting the ability to draw conclusions on specific cancers.

CANCER TREATMENT AND IBD

While data on the risk of new or recurrent cancer under immunosuppression in patients with IBD and

a history of cancer is limited, though increasing, considerably less is known regarding the effects of cancer treatment on IBD, and the effect of IBD and medications for IBD on important cancer outcomes.

Effect of cancer treatment on IBD

In a study from the Massachusetts General Hospital, 84 patients with IBD and extra-intestinal cancer were assessed for the effect of cancer treatment on the course of IBD[48]. The authors found that 66.7% of patients with active IBD at their cancer diagnosis experienced remission from IBD thought secondary to cytotoxic chemotherapy. Conversely, 17.4% of patients in remission from IBD at their cancer diagnosis experienced a flare during or within 5 years after their cancer treatment[48]. In the remission group, the authors found the risk of flare to be greatest among patients who received hormonal therapies (combination cytotoxic chemotherapy with adjuvant hormone therapy HR = 12.25, 95%CI: 1.51-99.06; hormone monotherapy HR = 11.56, 95%CI: 1.39-96.43). This suggests that hormonal therapies for cancer, such as breast and prostate, may increase the risk of IBD reactivation or counter the protective effects of cytotoxic chemotherapy[48]. A majority of patients with active IBD at their cancer diagnosis appeared to benefit from cancer treatment in the form of IBD remission, which was much more likely if the cancer treatment included cytotoxic chemotherapeutics and less likely if patients were treated with hormonal monotherapy[48].

In this cohort, there was no appreciable modification in IBD medications after a diagnosis of cancer. TNF-α antagonists were continued in three patients and the proportion of patients maintained on immunomodulators decreased slightly from 22% to 14% after a cancer diagnosis[48]. These data, however, were not compared to a control group of patients without chemotherapy or without cancer to assess whether patients with IBD and extra-intestinal cancer experienced a course of IBD different from patients without chemotherapy or cancer.

However, other studies have demonstrated a major modification in IBD medications after a diagnosis of cancer. In a study from a French clinical prospective database, a diagnosis of extra-intestinal cancer had a marked impact on the management of IBD, but was not associated with significant modifications in activity of IBD[49]. A diagnosis of extra-intestinal cancer led to some changes in therapeutic strategy, with a lesser use of thiopurines (19% *vs* 25%, $P < 0.001$) and an increased use of intestinal surgery (4% *vs* 2.5%, $P = 0.05$)[49].

Effect of IBD on cancer

Little is known regarding specific cancer outcomes in patients with IBD. Oncologists have generally been reluctant to administer pelvic irradiation in the setting of IBD, as the tolerance of pelvic irradiation in these patients is largely unknown. There exists only one study in the literature from Green *et al*[50] which retrospectively examined 47 patients with IBD and rectal cancer treated over a 34-year period (1960-1994) from the Mount Sinai Hospital, New York. The authors found a five-year overall survival rate of 42% and disease-free survival of 43%, which were comparable to results published for non-IBD-associated rectal cancer at that time, however, patients with high-grade tumors had statistically lower rates[50]. Complications, such as gastrointestinal morbidity or small bowel obstruction, were comparable to those reported in several large randomized trials of adjuvant chemoradiation therapy in rectal cancer arising in the general population[50].

In terms of chemotherapy and associated cancer outcomes, a small study on 8 patients with IBD and gastrointestinal malignancy showed that the most common gastrointestinal adverse event was diarrhea, with 38% of patients experiencing greater than 7 stools per day over baseline and/or fecal incontinence, all of which occurred in patients with CD[51]. Several studies have examined the effect of IBD medications on cancer outcomes. Multiple studies have demonstrated a role of anti-TNF-α in improving cachexia and increasing chemotherapy tolerance in patients with non-small cell lung cancer, renal cell carcinoma, and pancreatic cancer[52-54]. Moreover, in patients treated with TNF-α antagonists, the occurrence of cancer during treatment was not associated with a worse prognosis, and may even have a protective effect by reducing aggressive metastatic breast cancers at a cellular level[55,56].

Immunotherapies for cancer and immune-related colitis

Immunotherapy for cancer has shown promise in cases refractory to conventional treatment. However, unguided immune stimulation in cancer patients presents its own challenges. There are several reports of anti-cytotoxic T-lymphocyte-associated protein-4 antibodies used for melanoma, such as ipilimumab, and programmed cell death-1 receptor inhibitors used for melanoma and non-small cell lung cancer, such as and nivolumab, producing an immune-related colitis that is remarkably similar to IBD[57,58]. These medications, particularly when used in combination, result in clinical symptoms, endoscopic manifestations, and pathologic cellular infiltrates that emulate IBD. Fortunately, the majority of these cases respond to conventional treatments for IBD such as systemic corticosteroids, budesonide, and infliximab[57,58].

In a recent study, 50% of patients with advanced melanoma and baseline autoimmune disease, such as rheumatoid arthritis, IBD, and psoriasis, experienced either autoimmune exacerbations or immune-related adverse reactions when treated with ipilimumab[59]. These reactions were generally manageable with standard treatment including corticosteroids and infliximab[59]. As the field of immunotherapy for cancer

evolves, we may see an increase in immune mediated colitis, which highlights the important role for T-cell checkpoint inhibitors in exacerbating IBD or causing an IBD-like colitis.

CONCLUSION

Patients with IBD are at an increased risk of cancer secondary to long-standing intestinal inflammation and secondary to immunosuppressive therapies. As the population of patients with IBD ages, there is an increasing risk of cancer development. Many of these patients will require cancer treatment and many will require further treatment for their IBD.

Much research is being devoted to exploring the role of chronic intestinal inflammation from IBD in carcinogenesis, and the role of immunosuppressive medications used to treat IBD in the promotion and prevention of cancer. Despite these efforts, much remains unknown regarding the interaction between IBD, medications for IBD, and cancer treatment, and the risk of cancer recurrence in patients with IBD and a history of cancer.

Understanding the effects of chemotherapy, hormonal therapies, radiation, and surgery for cancer on IBD may help identify patients at the highest risk for disease exacerbation during and after specific cancer treatments, especially in those who may require re-initiation of immunosuppressive therapies for IBD. In addition, while retrospective data has demonstrated some evidence for the safety of immunosuppression in patients with IBD and a history of cancer, prospective data are needed to validate these findings. Furthermore, data is lacking regarding specific cancers, treatments, and risk of recurrence under varying immunosuppressive medications for IBD. More data will permit the development of evidence-based, quantitative risk-benefit models including cancer and IBD-related variables to assist clinicians in managing this complex patient population.

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