ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Treating Patients With Inflammatory Bowel Disease During and After Cancer

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G&H What is the risk of cancer in patients with inflammatory bowel disease?

JA Individuals with inflammatory bowel disease (IBD) are at an increased risk of cancer secondary to longstanding intestinal inflammation as well as immunosuppressive therapies. As the IBD population ages, there is a rising risk of cancer development. Regarding specific cancers, individuals with IBD are at an increased risk of developing intestinal neoplasia, especially colorectal neoplasia, colorectal dysplasia, and colorectal cancer (CRC), as a consequence of chronic colonic inflammation. CRC rates have recently been found to be decreasing among IBD colitis patients, with the cancer occurring in 1%, 2%, and 5% of patients 10, 20, and more than 20 years, respectively, from the initial diagnosis of IBD. Reasons for this decline are multifactorial but are likely because of a combination of factors, including improved endoscopic surveillance and medical therapies. Other possible intestinal malignancies in the IBD population include small bowel adenocarcinoma, intestinal lymphoma, and anal cancer, all of which are very rare and are primarily found in individuals with Crohn's disease.

In addition, patients with IBD have been shown to be at increased risk of developing extraintestinal malignancies, including cholangiocarcinoma, skin cancers, hematologic malignancies, genitourinary cancer, cervical cancer, and prostate cancer. These malignancies may be consequences of immunosuppressive therapies and an underlying inflammatory state. Cholangiocarcinoma is 4 times more likely to develop in individuals who have IBD compared with those who do not have the condition, with the risk mainly being driven by concomitant primary sclerosing cholangitis. This concomitant condition elevates the risk of cholangiocarcinoma over 150-fold compared with patients who do not have it, for a lifetime risk of 5% to 10%.

G&H Which drugs used to treat IBD have been associated with an increased risk of cancer?

JA Several IBD therapies have been associated with specific cancers. In IBD patients receiving thiopurine therapy, there is a 2-fold increased risk of nonmelanoma skin cancers such as basal cell and squamous cell cancers. It is thought that this risk continues even after discontinuing thiopurine therapy, although to a lesser extent. Thus, annual dermatologic examinations are important in patients with IBD who are currently using thiopurines or previously did. Lymphoma is another risk associated predominantly with thiopurine therapy. A recent meta-analysis found that the standardized incidence ratio of lymphoma ranged from 2.8 to 9.2 among IBD patients receiving thiopurines compared with those patients who were not exposed to such therapy. Although most lymphomas related to IBD involve B cells, hepatosplenic T-cell lymphoma is a risk for men less than 35 years of age. This lymphoma is associated with the long-term use of thiopurines, often in combination with anti–tumor necrosis factor (TNF) agents, and is frequently fatal. Patients who have not been exposed to Epstein-Barr virus are also at risk for a rare but related lymphoma when acutely infected and maintained on thiopurines. Additionally, very limited data suggest an association between current thiopurine use and an increased risk of acute myeloid leukemia, myelodysplastic syndromes, and genitourinary cancers.

Data linking the use of anti-TNF monotherapy with lymphoma and melanoma are conflicting, but there may be a small increased risk. Data have not suggested that

patients with IBD treated with Janus kinase inhibitors have an increased risk of malignancy. However, clinical trials of tofacitinib in rheumatoid arthritis patients older than 50 years have shown an increased risk of any malignancy, especially nonmelanoma skin cancers, lung cancer, and lymphoma, compared with patients receiving anti-TNF therapy. Further data are needed in patients with IBD to evaluate such risk more firmly. Although current evidence does not demonstrate an increased risk of malignancy in IBD patients being treated with vedolizumab (Entyvio, Takeda), ustekinumab, risankizumab (Skyrizi, AbbVie), mirikizumab (Omvoh, Lilly), guselkumab (Tremfya, Janssen), ozanimod (Zeposia, Bristol Myers Squibb), and etrasimod (Velsipity, Pfizer), there is a lack of long-term data.

G&H What has research shown regarding the effects of immunosuppression in IBD patients with cancer?

JA Given the association between malignancies and immunosuppressants, there is concern that IBD treatments may increase the risk of incident cancer. However, recent data have not supported any increased risk. Thus far, prospective data have reassured that IBD treatments are not associated with a significant increased risk of incident cancer in patients who have IBD and a history of cancer. This has been confirmed by preliminary data from the ongoing SAPPHIRE registry. Out of 305 IBD patients with prior cancer, 210 were exposed to subsequent immunosuppression. During a median follow-up of 4.8 years, 46 patients developed subsequent cancers (25 new, 21 recurrent). A proportional hazards model adjusting for demographic and clinical factors found no significant association between receiving immunosuppression and incident cancer, nor with any of the major drug classes. Results are awaited from the ongoing I-CARE registry of patients with a history of cancer who were exposed to anti-TNF therapy or vedolizumab.

G&H Has exposure to IBD therapy been shown to impact cancer outcomes?

JA Although there are many data evaluating the risk of malignancy associated with immunosuppressive therapy in patients who have IBD as previously noted, less is known regarding the impact of IBD therapies on cancer outcomes. Owing to the perceived theoretical risk of the toxicity of cancer treatment (including chemotherapy, radiation, and surgery), there are many studies that show patients with IBD may be undertreated for their cancers. Pivotal randomized controlled trials and long-term safety registries have little to no data on IBD patients with active cancer, and smaller observational studies have commonly excluded patients with active cancer. A retrospective, multicenter study evaluating the safety of IBD-directed immunosuppressive therapy in patients who had active or recent prior cancer found similar rates of cancer progression in patients who were exposed to TNF antagonists vs non-TNF biologics vs immunomodulator monotherapy. Emerging data suggest that certain IBD therapies may reduce the positive impact of immune checkpoint inhibitors—including cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) inhibitors—on cancer, but more data are needed. If IBD activity needs to be controlled in patients who have active cancer and are receiving oncologic treatment, the use of IBD therapies (including biologic agents) is warranted, with close collaboration recommended between the treating oncologist and gastroenterologist.

G&H Has cancer therapy been shown to affect the course of IBD?

JA Yes, cancer therapy may affect the course of IBD. IBD treatment decisions in patients who develop cancer are nuanced. It is important to take into consideration the burden of symptoms and the possibility of inadequate IBD treatment decreasing quality of life and affecting the tolerability of cancer treatment. Retrospective studies of patients with active IBD and extraintestinal cancers found that patients may achieve remission of their IBD if they are receiving cytotoxic chemotherapy, suggesting a beneficial impact on intestinal inflammation. In contrast, an increased risk of IBD relapse was associated with hormonal deprivation therapy, whether used by itself or combined with cytotoxic chemotherapy. Further evidence is needed to clarify the effects of hormonal deprivation therapy on IBD course and development. Nevertheless, gastroenterologists should closely follow patients who are diagnosed with cancers typically treated with hormone deprivation therapy, as these patients may be at increased risk for IBD reactivation. Pelvic radiation is another area of study with conflicting data regarding IBD relapse. Immune checkpoint inhibitors commonly cause colitis. In patients known to have IBD, checkpoint inhibitor treatment can increase the risk of IBD relapse. A meta-analysis found that such treatment led to relapse of IBD in 40% of patients, with biologics being needed in at least one-third. CTLA-4 inhibitors were associated with a higher risk of IBD relapse compared with PD-1 and PD-L1 inhibitors.

G&H How can immune checkpoint inhibitor colitis be best managed?

JA In general, checkpoint inhibitor colitis is treated as underlying IBD colitis would be, with corticosteroids and then biologics and/or small molecules for corticosteroid-refractory patients. The most data are available for anti-TNF agents and vedolizumab, but there are supportive data for all biologics and small molecule IBD therapies. Although there are emerging data that certain IBD therapies (such as anti-TNF agents) may reduce the positive impact of immune checkpoint inhibitors on cancer treatment, checkpoint inhibitor colitis should be managed aggressively given its significant morbidity.

G&H What guidance would you offer about managing IBD patients who have cancer or who have a fear of developing cancer from IBD therapies?

JA Because of very limited data, it is difficult to offer clear guidance regarding IBD medication management in individuals with IBD who develop cancer. The biggest concern lies with thiopurines and anti-TNF agents; data are insufficient for altering the use of other IBD therapies. Because there is an increased risk of lymphoma and nonmelanoma skin cancers with thiopurines, such treatment should be discontinued if a patient develops lymphoma. There should also be consideration of stopping thiopurines if patients develop multiple or recurrent nonmelanoma skin cancers. The development of melanoma or lymphoma in a patient receiving anti-TNF therapy warrants consideration of stopping the therapy as well. Usually, oncologists defer to gastroenterologists regarding IBD-directed immunosuppression during the treatment of cancer, underscoring the importance of understanding the relationship between IBD activity and cancer treatments.

Additionally, it is important to reassure patients that the risk of cancer from IBD therapies is extremely low, although the risk of cancer from uncontrolled inflammation may be significantly higher. Fear of cancer associated with treatment should be openly and thoroughly addressed in shared decision-making. If cancer does develop—as it can in the general population—it requires coordinated, multidisciplinary care and close monitoring.

G&H How can patients with prior cancer be best monitored while being treated for IBD?

JA Patients who have IBD and a history of cancer should be monitored through a multidisciplinary approach involving gastroenterologists and oncologists. Monitoring should be individualized based on cancer type, stage, time since remission, and prior therapies. It is important to remember that the risk of cancer recurrence is most strongly influenced by cancer type and stage, not by IBD therapy exposures. Cancer surveillance should follow standard guidelines for the original cancer type, with special attention to colorectal cancer screening in IBD and dermatologic examinations. Regular clinical assessments, laboratory monitoring, and shared decision-making are essential, especially when reintroducing IBD therapies. Enrolling patients in registries such as SAPPHIRE can help inform long-term safety and guide future care.

G&H What further research is needed?

JA The relationship between IBD and cancer is an evolving area of research. As mentioned, there is an increasing risk of cancer development as the IBD population ages. Many of these patients will require cancer treatment, and many will require further treatment for their IBD. Questions remain regarding the relationship between IBD, IBD therapies, cancer, and cancer treatment, as well as the risk of cancer recurrence in patients who have IBD and a history of cancer. Overall, data are lacking regarding specific cancers, treatments, and the risk of recurrence with different therapies for IBD. More data from prospective registries, such as SAPPHIRE, will enable 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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Suggested Reading

Axelrad JE, Hashash JG, Itzkowitz SH. AGA clinical practice update on management of inflammatory bowel disease in patients with malignancy: commentary. *Clin Gastroenterol Hepatol*. 2024;22(7):1365-1372.

Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med*. 2015;372(15):1441-1452.

Faye AS, Holmer AK, Axelrad JE. Cancer in inflammatory bowel disease. *Gastroenterol Clin North Am*. 2022;51(3):649-666.

Hong SJ, Zenger C, Pecoriello J, et al. Ustekinumab and vedolizumab are not associated with subsequent cancer in IBD patients with prior malignancy. *Inflamm Bowel Dis*. 2022;28(12):1826-1832.

Itzkowitz SH, Jiang Y, Villagra C, et al; New York Crohn's and Colitis Organization. Safety of immunosuppression in a prospective cohort of inflammatory bowel disease patients with a history of cancer: SAPPHIRE registry. *Clin Gastroenterol Hepatol*. 2025;23(5):855-865.e5.

Kimmel J, Axelrad J. The complex interplay between inflammatory bowel disease and malignancy. *Curr Gastroenterol Rep*. 2020;22(3):13.

Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis*. 2013;19(4):789-799.