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Using Immunosuppressive Therapies to Treat Inflammatory Bowel Diseases (IBD) in the Post-Cancer Setting

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Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD), and ulcerative colitis (UC), are chronic immune-mediated inflammatory disorders (IMID) affecting both intestinal and extraintestinal organs. Chronic intestinal inflammation causes multifocal DNA damage,[1-3] increasing the risks of intestinal cancers.[4,5] While the widespread use of effective biologic and small molecule therapies and intensified immune modulating (IM) regimens in recent years may have contributed toward declining colorectal cancer risks,[6] these treatments could have introduced unexpected cancer risks in organs not directly affected by IBD due to reduced immune surveillance. Among individuals with IBD, the use of thiopurines has been frequently associated with risks of lymphoma,[7-9] non-melanoma skin cancer (NMSC),[10-12] and cervical cancer.[13] Several large studies have also reported increased risks of lymphoma,[8] and melanoma[14,15] associated with anti-tumour necrosis factor alpha (anti-TNF) therapies, although other studies have not shown these associations.[16] A randomized controlled trial (RCT) in elderly individuals with rheumatoid arthritis (RA) and cardiovascular risk factors reported a slightly increased all-cause cancer risk with the non-selective Janus kinase inhibitor (JAKi), tofacitinib.[17] Other immunosuppressive (IS) therapies, including methotrexate, anti-interleukin (IL)-12/23 or anti-IL-23 therapies,[18-20] anti-α4β7 integrin therapy,[21,22] JAK-1-selective inhibitors (upadacitinib),[23,24] and sphingosine-1-phosphate receptor agonists,[25-27] have not been associated with increased cancer risks to date. However, some of these newer therapies have only been available for a few years.

Given the low absolute risk of treatment-related cancers, controlling underlying IBD with IS therapies is typically prioritized to improve quality of life and reduce IBD-related complications. However, the decision to start or continue IS therapy in individuals with current or prior malignancy is more complex, as immune surveillance may be more crucial for these patients. Clinical trials generally exclude patients with a cancer history, which limits the available evidence on cancer recurrence risks associated with specific therapies. Additionally, some cytotoxic chemotherapy regimens can control IBD for prolonged periods,[28] suggesting that additional immunomodulation may be unnecessary, and potentially harmful, during cancer treatment. Conversely, hormonal, radiation, and immune checkpoint inhibitor therapies have been associated with increased risks of IBD flares.[29,30] Therefore, a careful and collaborative approach with oncologists is essential for the optimal management of IBD patients diagnosed with cancer.

Recently, the European Crohn's and Colitis Organization (ECCO)[31] and the American Gastroenterological Association (AGA)[32] released practice recommendations regarding the use of IS therapies in individuals with IBD in the post-cancer setting. This review summarizes the evidence regarding cancer risks associated with specific IBD therapies in this context and presents a management approach based on both scientific and practical considerations.

Methotrexate and Thiopurines

Methotrexate (MTX) and thiopurines (azathioprine and 6-mercaptopurine) are anti-metabolites that act as non-selective IM by interfering with DNA synthesis.[33,34] A meta-analysis of 16 studies, including 11,702 individuals with IMIDs (IBD, RA, psoriasis), and 3,706 with IBD, followed for an average of 3 years post-cancer diagnosis, found no significant increase in new or recurrent non-dermatological cancers among patients continuing IM vs. anti-TNF therapy or no IM therapy (36.2, 33.8, and 37.5 per 1000 patient years [PY], respectively). However, there was a slight increase in the rate of new or recurrent skin cancers among those who continued immunosuppression compared to those who discontinued it (71.6 vs 50.8/1000 PY).[35] A retrospective study of 54,919 IBD patients with prior basal cell carcinoma (BCC) found that thiopurine use was associated with an increased risk of BCC recurrence compared to 5-ASA therapy (adjusted hazard ratio [aHR] 1.65, 95% confidence interval [CI] 1.24–2.19).[36]

Based on the limited data, ECCO concluded that there is insufficient evidence regarding the safety of methotrexate use following a cancer diagnosis. Both ECCO[31] and AGA[32] suggested discontinuing thiopurine therapy in patients with active malignancy and considering alternatives in individuals with a history of lymphoma, NMSC, or cervical cancer.

Anti-TNF Therapy

Anti-tumour Necrosis Factor (TNF) therapies (infliximab, adalimumab, golimumab, certolizumab) were the first biologic treatments introduced for CD and UC. Despite concerns about inhibiting a cytokine involved in tumour clearance, anti-TNF therapies have generally not been associated with increased cancer risks,[16] except for a few isolated reports relating to lymphoma[8] and melanoma.[14,15]

In the aforementioned meta-analysis of 16 studies, no increase in cancer recurrence was observed in IBD patients who remained on anti-TNF therapy compared to those who discontinued IM agents.[35] Another retrospective study of 463 IBD patients diagnosed with cancer found no increase in new or recurrent cancer in those who continued or were newly started on anti-TNF therapy, compared to those who did not receive IM agents over a 6.2-year median follow-up.[37] Additionally, a multicentre retrospective cohort of 538 IBD patients with a history of non-digestive cancers found no difference in the incident cancer-free survival rates between patients treated with anti-TNF therapy or vedolizumab over a median follow-up of 55 months.[38] Furthermore, a population-based study of 25,758 IMID patients from Denmark found no significant increase in cancer rates among IBD patients on anti-TNF therapy (30.3/1000 PY) compared to those not on therapy (34.4/1000 PY).[39]

Based on the above, ECCO suggests that anti-TNF therapy may be used in patients with current or prior cancer, although data on specific cancer types are lacking.[31] In contrast, the AGA recommends stopping anti-TNF therapy indefinitely for patients with a history of melanoma or hematologic cancers but continuing it for patients with other cancer types.[32]

Vedolizumab

Vedolizumab, a gut-selective α4β7 integrin inhibitor, has shown an excellent overall safety profile in treating UC and CD.[40] Follow-up data from clinical trials have not indicated an increased risk of malignancy with vedolizumab.[21] A retrospective study of 538 IBD patients with non-digestive cancers found no difference in cancer-free survival rates between patients treated with anti-TNF therapy or vedolizumab compared to those not receiving IM therapy.[38] Additionally, another study of 463 IBD patients with a history of cancer found that vedolizumab was associated with a lower rate of new or recurrent cancers (2.2/1000) compared to anti-TNF therapy (4.2/1000) and no IM effects (5.6/1000).[37]

ECCO[31] and AGA[32] recommend continuing vedolizumab in the post-cancer setting. However, decisions made during active cancer, particularly gastrointestinal cancers, should be individualized due to the lack of evidence.

Anti-IL12/23 and Anti-IL23

Anti-IL-12/23 antibodies (ustekinumab) and anti-IL-23-specific (rizankizumab, mirikizumab, guselkumab) antibodies have shown efficacy and have an excellent safety profile in treating UC and CD.[18,41,42] Long-term registry data from psoriasis and psoriatic arthritis have not demonstrated an increased risk of malignancy with these agents.[20,29] A retrospective study of 341 IBD patients with a cancer history found no significant difference

in cancer incidence between those treated with ustekinumab and those treated with anti-TNF therapy (aHR 5.23, 95% CI 0.96–28.41) or no IM therapy (aHR 0.88, 95% CI 0.25–3.03) over a median follow-up of 5.4 PY.[43] Data on anti-IL-23 therapies is limited, as these agents have only recently become available for IBD.

Based on the limited data, ECCO recommends continuing anti-IL12/23 therapy in patients with a history of malignancy but makes no specific recommendations for its use during active malignancy.[31] Similarly, AGA recommends not changing anti-IL12/23 or anti-IL23 therapy in patients with prior cancer.[32]

Other Therapies

JAKi and sphingosine-1-phosphate receptor agonists are becoming more common in IBD management. To date, no studies have evaluated the cancer risks associated with these therapies in the post-cancer setting. ECCO and AGA currently do not recommend changing these therapies for patients with active or prior cancer.

Cancer Recurrence Risks Across Multiple IS Therapies

A prospective cohort study of 405 IBD patients with a prior cancer diagnosis found no association between IM use at the time of study entry and the risk of new or recurrent cancers.[44] Similarly, a large registry study (SAPPHIRE) of 305 IBD patients with a history of cancer found no significant difference in cancer recurrence between those who received IM therapy (2.58/100 PY) and those who did not (4.78/100 PY) (aHR 1.41, 95% CI, 0.69–2.90) over a median follow-up of 4.8 years.[45]

Two meta-analyses involving IMID patients (11,702 and 3,266 patients, respectively) have also shown no statistical difference in cancer recurrence risks based on the timing of IM therapy (IM therapy started within versus more than 5 or 6 years from the index cancer diagnosis (33.6 vs 32.9/1000 PY for IM, p=0.86, and 43.7 vs 21.0/1000 PY for anti-TNF, p=0.43).[35] Similarly, the rates were 22 vs 48/1000 PY for IM and 32 vs 32/1000 PY for anti-TNF, (p>0.1 for all).[46]

Recommendations for IBD Treatment in the Post-Cancer Setting

In the post-cancer setting, the decision to initiate or continue IM therapy should consider the relative risks of cancer recurrence versus IBD relapse. The early post-cancer setting (within 5 years of cancer diagnosis) is generally considered a more critical period for cancer recurrence, although two meta-analyses found no significant difference in cancer recurrence based on whether IM therapy was started within 6 years or more than 6 years after cancer diagnosis.[35,46]

In some situations, managing IBD may be as important, if not more so, than the cancer recurrence risk, particularly for those with complicated IBD phenotypes (e.g., penetrating or extensive small bowel CD, complex perianal fistulizing CD, or severe pancolitis) or those with palliative cancer who prioritize quality of life. Furthermore, the type of cancer and cancer treatment regimen play a significant role in determining the appropriate IM therapy, necessitating a collaborative approach with oncologists.

The Penn Classification system, which was developed to describe rates of cancer recurrence in solid organ transplant recipients, can help guide the management of IM in post-cancer IBD patients. It is important to recognize that the IM regimens used in the post-transplant setting differ from those used in IBD. According to this system, low-risk cancers (e.g., lymphoma, thyroid, cervical, and testicular cancers) have less than a 10% chance of recurrence, while intermediate-risk cancers (e.g., uterine, breast, prostate, lung, and gastrointestinal cancers) have an 11–25% recurrence risk, and high-risk cancers (e.g., bladder, renal, melanoma, NMSC, sarcoma, multiple myeloma) have over a 25% recurrence risk.[47]

Based on the available evidence, we recommend avoiding thiopurines in individuals with lymphoma, NMSC, or cervical cancer, and to withhold them for at least 5 years after alternate cancer diagnoses. Given the limited utility of thiopurines in managing IBD, their continued use should be carefully considered on a case-by-case basis. Anti-TNF therapy should be withheld for up to 5 years after a lymphoma or

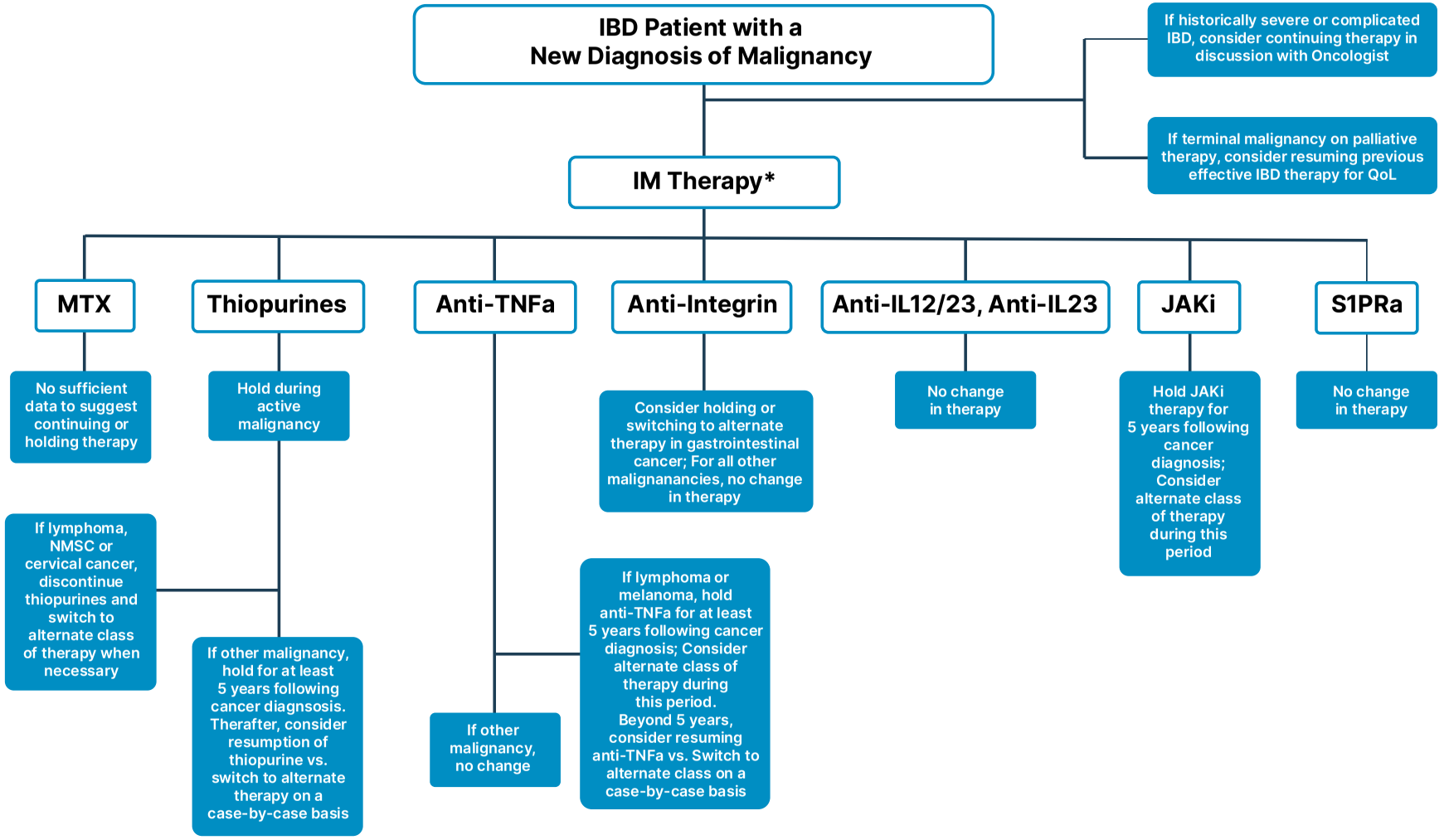

Figure 1. Putative care pathway to manage immunosuppressive therapies following cancer diagnosis in individuals with IBD; *courtesy of Rana Kandel, MD and Sanjay K. Murthy, MD, MSc, FRCPC.*

Abbreviations: IBD: inflammatory bowel diseases, **IL:** interleukin, **IM:** Immunomodulating, **JAKI:** Janus kinase inhibitors, **NMSC:** Non-Melanoma Skin Cancer, **MTX:** Methotrexate, **QoL:** quality of life, **S1PRa:** Sphingosine-1-Phosphate Receptor agonists, **TNF:** anti-tumour Necrosis Factor.

melanoma diagnosis, and alternative therapies, such as anti-IL-23 or anti-integrin therapy, may be considered for these patients if necessary. Given the potential for increased risk of cancer in IMID patients treated with non-selective JAKi, we suggest withholding this class of treatment for up to 5 years following a cancer diagnosis. The decision to resume or switch to alternate therapy should be considered on an individual basis. This recommendation differs from ECCO and AGA but is in line with that of other groups.[48] We also suggest reassessing anti-integrin therapy in patients who develop gastrointestinal malignancies. For all other IM classes, there is no compelling data to suggest holding or switching therapy. However, holding therapy may be reasonable in patients receiving cytotoxic chemotherapy expected to control systemic inflammation or in those with a prior cancer that has a moderate to high risk of recurrence (**Figure 1**).

Conclusion

With a growing armamentarium of IBD therapies, their increasing use at higher doses and earlier in the disease course, and an IBD population that is living longer, gastroenterologists will encounter an increasing number of IBD patients with active or prior cancer. We have summarized the available evidence and proposed a management approach in this setting to guide shared decision-making in practice. However, it is important to note that nearly all the existing data are based on observational studies and the number of large studies in the post-cancer setting, particularly for newer agents, is limited. As such, optimal management in this area requires a collaborative, dynamic approach, with no "set in stone" solutions. Future large multi-centre studies evaluating specific cancer risks associated with specific therapies are required to better guide IBD treatment in this setting.

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