Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents

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Q5 **BACKGROUND & AIMS:** **Our understanding of malignancy associated with immunosuppression in patients with inflammatory bowel disease (IBD) comes from studies of individuals with no history of cancer. We investigated whether patients with IBD and a history of cancer who were subsequently immunosuppressed have an increased risk of developing incident cancer.**

METHODS: **We performed a retrospective analysis of data from 333 patients with IBD treated at 7 academic medical centers who developed cancer and subsequently received treatment with anti–tumor necrosis factor (TNF), anti-TNF with an antimetabolite (thiopurines, methotrexate), antimetabolites, or no subsequent exposure to immunosuppressive agents (controls). We collected data on their primary outcomes of incident cancers (new or recurrent). Hazard ratios (HRs) were calculated by using Cox proportional hazards and Kaplan-Meier survival curves; study groups were compared by using the log-rank test.**

RESULTS: **During the follow-up period, 90 patients (27%) developed an incident cancer. Patient characteristics between groups differed, but matching was not possible because of the relatively small sample sizes. There was no difference in time to incident cancer ($P = .14$) or type of incident cancer ($P = .61$) among the 4 groups. After adjusting for recurrence risk for type of prior cancer, there was no difference in risk of incident cancer (HR for anti-TNF, 0.32; 95% confidence interval [CI], 0.09–1.09; HR for anti-TNF with an antimetabolite, 0.64; 95% CI, 0.26–1.59; HR for an antimetabolite, 1.08; 95% CI, 0.54–2.15) or time to subsequent cancer between study arms ($P = .22$).**

CONCLUSION: **On the basis of a retrospective study, in patients with IBD and a history of cancer, exposure to an anti-TNF agent or an antimetabolite after cancer was not associated with an increased risk of incident cancer, compared with patients who did not receive immunosuppression. Larger, matched, prospective studies are needed to confirm these findings.**

Keywords: Crohn's Disease; Ulcerative Colitis; Drug; Tumor.

Abbreviations used in this paper: **CESAME, Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.**

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Immunomodulators and biologic agents (collectively, immunosuppression) are effective in treating patients with inflammatory bowel disease (IBD), and recent evidence supports their introduction earlier in the disease course.[1,2] Patients and physicians often weigh the risk of active IBD against the adverse effects of immunosuppression, especially therapy-associated malignancies. Most of our understanding about the rates and types of malignancy associated with the use of immunosuppression in patients with IBD comes from studies of individuals who had no history of cancer.[3] Little is known about the risk of subsequent malignancy in IBD patients with a prior diagnosis of cancer who are exposed to immunosuppressive agents.

Antimetabolite immunosuppressive agents such as thiopurines and methotrexate may promote the development and recurrence of cancer by a variety of established mechanisms including alteration in DNA, activation of oncogenes, reduction in physiologic immunosurveillance, and facilitation of the action of oncogenic viruses.[4–6] Less is known about the potential malignancy-promoting potential of biologic therapies that block the action of tumor necrosis factor-alpha (TNF-α). The effect of TNF-α in inflammation-associated carcinogenesis is unpredictable. TNF-α has been shown to exhibit anti-tumor effects by initiating cellular apoptosis of malignant cells, but conversely, it is secreted by most tumors to facilitate cellular survival and enhance neoplastic proliferation as a pro-tumorigenic inflammatory cytokine.[7–10]

Previous studies have demonstrated an increased risk of lymphoma in patients exposed to thiopurines and primary melanoma and non-melanoma skin cancer in patients exposed to thiopurines and anti-TNF-α therapies.[11–19] Because of these risks, patients with a history of cancer within 5 years have typically been excluded from randomized controlled trials of anti-TNF-α therapy in IBD because of the theoretical risk of therapy-associated malignancies. In addition, oncologists and gastroenterologists generally suspend immunosuppression for IBD while patients undergo chemotherapy and often continue to withhold therapy while patients are in remission from cancer. However, withholding or reducing IBD treatment for cancer may worsen IBD and, in certain situations, hinder appropriate cancer management.[20]

To date, there is a lack of substantial clinical data on the management of IBD after a diagnosis of cancer. The Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France (CESAME) group found that in patients with IBD, exposure to immunosuppression was independently associated with the development of cancer, but it did not increase the risk of new or recurrent cancer in those with a history of cancer.[21] Because of the limited number of patients with IBD and a history of cancer with subsequent exposure to biologics agents in the CESAME study, this conclusion only applied to thiopurine exposure, and no conclusions could be drawn regarding anti-TNF-α therapies.[21]

The objective of this study was to investigate whether IBD patients with a history of cancer who were subsequently exposed to immunosuppression were at an increased risk of developing incident cancer, new or recurrent.

Methods

After Institutional Review Board approval at each participating site, electronic medical records from 8 academic medical centers affiliated with the newly established New York Crohn's and Colitis Organization and Massachusetts General Hospital were identified on the basis of a diagnosis of IBD and cancer. The data obtained from each site's electronic medical record included patients drawn from a variety of geographically separate clinical sites (major hospital, outpatient clinical centers, endoscopy/same-day surgery centers, private practices with admitting privileges at academic centers, etc). A standardized data reporting template was established for all sites to enter data. A diagnosis of IBD was based on accepted criteria including clinical symptoms, endoscopy, radiology, pathology, and operative reports. All chart reviews were performed by trained clinicians. Patients were then categorized on the basis of subsequent medication exposure after a diagnosis of cancer if they had at least 1 follow-up encounter documenting treatment with the following: anti-TNF-α (anti-TNF-α arm), anti-TNF-α with a thiopurine or methotrexate (combination arm), thiopurines or methotrexate (antimetabolite arm), or no subsequent immunosuppression exposure (control arm).

Charts were reviewed for basic demographic information, age at IBD diagnosis, IBD subtype, date of cancer diagnosis, type and stage of cancer, cancer risk type, cancer treatment, date of last clinical encounter, and IBD medication exposure and duration before and after cancer diagnosis. For patients with subsequent incident cancer (defined as new or recurrent), charts were reviewed for date of diagnosis, type, stage, risk type, and treatment. Cancer type was categorized into gastrointestinal (any malignancy of the luminal gastrointestinal tract), hematologic (any leukemia or lymphoma), dermatologic (melanoma and non-melanoma skin cancers), or other solid organ. Cancer risk type was categorized on the basis of Penn's classification for recurrence risk of preexisting malignancies as follows: low-risk malignancies include incidental renal tumors, lymphomas, testicular, uterine, cervical, and thyroid carcinomas; intermediate-risk cancers include carcinomas of the uterine body, Wilms tumors, and carcinomas of the colon, prostate, and breast; and high-risk malignancies include carcinomas of the bladder, sarcomas, malignant melanomas, symptomatic renal carcinomas, non-melanoma skin cancers, and myelomas.[22]

The primary outcome was development of incident cancer. Time to incident cancer was calculated from the