

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Risk of Lymphoma in Patients with Inflammatory Bowel Disease



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G&H How frequently does lymphoma occur among patients with inflammatory bowel disease?

JDL Lymphoma is one of the 10 most common cancers in the United States, but the likelihood of any particular individual being diagnosed with lymphoma is still relatively low. The incidence of lymphoma in the general population ranges from approximately 15 cases per 100,000 people per year to 100 cases per 100,000 people per year, depending on the patient's age. In the absence of immunosuppressive therapies, patients with inflammatory bowel disease (IBD) probably have, at most, only a very slightly increased risk of lymphoma compared to the general population.

G&H What are the major risk factors for the development of lymphoma in patients with IBD?

JDL Drawing on experience in other populations, we know that immunosuppression is an important factor in the development of lymphoma. Patients with AIDS have a higher incidence of lymphoma than the general population, and rates of lymphoma are also very high in organ transplant recipients who are taking immunosuppressive medications to prevent rejection. For example, patients who have undergone cardiac transplantation require very high levels of immunosuppression, particularly in the first year after transplantation, and they have an extremely

high incidence rate of lymphoma compared to the general population. There is also evidence that immunosuppression, particularly use of thiopurines, increases the risk of lymphoma among patients with IBD.

G&H Which drugs or combinations of drugs have been associated with the highest risk of lymphoma?

JDL Data consistently show that the incidence of lymphoma is approximately 4-fold higher in patients treated with azathioprine and 6-mercaptopurine compared to patients who are not treated with these drugs. There is less evidence regarding most of the other drugs used to treat IBD. Studying the association between lymphoma and use of anti-tumor necrosis factor (anti-TNF) drugs is complicated because most patients treated with anti-TNF agents have been previously treated with azathioprine or 6-mercaptopurine; in some cases, patients are receiving both types of medication simultaneously. There is some evidence that combination treatment with thiopurines and anti-TNF agents might further increase the risk of lymphoma, but this conclusion is based on small studies and needs to be evaluated in larger populations.

Methotrexate is another systemic immunosuppressant that is used in the treatment of Crohn's disease and, to a lesser degree, in ulcerative colitis. Interestingly, there is less evidence that methotrexate increases the risk of lym-

phoma, although most of these data are from studies of patients treated with methotrexate for diseases other than IBD. However, methotrexate therapy in IBD patients is probably still associated with some increase in the risk of lymphoma. Specifically, there are reports of patients who have developed Epstein-Barr virus (EBV)-associated lymphoma in the setting of methotrexate treatment but then showed regression of the lymphoma when methotrexate therapy was discontinued. While the risk of lymphoma is probably somewhat increased with methotrexate, current evidence suggests that this risk is probably less than the risk associated with thiopurines and perhaps less than the risk associated with anti-TNF therapy.

G&H What studies have examined the association between lymphoma and IBD therapy?

JDL In 2005, my coworkers and I published a meta-analysis in which we pooled data from several studies; from this meta-analysis, we estimated that treatment with thiopurines increased the risk of lymphoma approximately 4-fold. The CESAME study from France, which was published in 2009, confirmed this finding in a large, prospective, cohort study; in this study, the authors observed an approximately 5-fold increase in the risk of lymphoma among IBD patients treated with azathioprine or 6-mercaptopurine. In addition to confirming that the risk of lymphoma is increased approximately 4-fold to 5-fold among patients treated with thiopurines, the CESAME study also found that, if patients had been treated with thiopurines in the past but were no longer taking these drugs, they did not have a higher incidence of lymphoma than patients who had never been treated with thiopurines. There is some uncertainty regarding this finding because only a few cases of lymphoma were observed in the subgroup of patients who had been previously treated with thiopurines. Nonetheless, this finding is very encouraging, as it suggests that the risk of lymphoma may return to baseline after thiopurine therapy is discontinued.

G&H Is there any indication that IBD itself increases patients' risk of lymphoma?

JDL There are several studies in patients with rheumatoid arthritis that show an association between the severity of the underlying disease and the incidence of lymphoma; in general, patients who have more severe rheumatoid arthritis are more likely to be diagnosed with lymphoma, independent of their medical therapies. Unfortunately, we have less data regarding the association between lymphoma and Crohn's disease or ulcerative colitis. My coauthors and I published a study many years ago in which we identified a

small number of patients who had lymphoma and Crohn's disease or ulcerative colitis, and we compared these patients to thousands of IBD patients who did not have lymphoma. In this study, both groups looked relatively similar in terms of recent steroid use and surgery.

Unfortunately, it is difficult to determine what role the inflammatory disease process might play in the etiology of lymphoma. On the one hand, clinicians tend to use systemic immunosuppressants such as thiopurines, anti-TNF therapies, and/or methotrexate more frequently in patients with difficult-to-control disease. However, patients who stay on these drugs for a long period of time often have fairly well-controlled disease while they are on these therapies. Thus, teasing out the role of inflammation versus the role of the medications is challenging.

Currently, we cannot definitively say that chronic inflammation does not play a role in the development of lymphoma. However, the incidence of lymphoma in the IBD patient population as a whole is about the same as the incidence of lymphoma in the general population, so low levels of inflammation probably do not have much of an effect on an individual's risk of developing lymphoma. Also, clinicians should keep in mind that, even though these medications may increase the risk of lymphoma, the magnitude of this increase is small, so the benefit of these medications outweighs the potential harm in most patients whose disease severity warrants chronic immunosuppression therapy.

G&H How do immunosuppressants increase the risk of lymphoma?

JDL There is a subset of lymphoma referred to as EBV-associated lymphoma, or post-transplantation lymphoproliferative disorder, that is probably caused directly by EBV infection.

A large proportion of the US population has been infected with EBV, even if they do not recall having mononucleosis; when these patients subsequently receive immunosuppressive drugs as a treatment for IBD, these drugs may cause the latent EBV infection to trigger lymphoma. Other mechanisms for the development of lymphoma are also possible in IBD patients who are receiving immunosuppressive therapy, but reactivation of EBV infection is the best-studied mechanism.

G&H Do IBD patients who are receiving immunosuppression therapy need to be monitored for lymphoma?

JDL In my practice, I do not perform any special surveillance for lymphoma, aside from taking a history of systemic symptoms and examining the patient for lymphadenopathy.

G&H If an IBD patient is diagnosed with lymphoma, should their immunosuppressive therapy be halted or changed?

JDL In the rare event that a patient develops lymphoma, the gastroenterologist should discontinue the patient's immunosuppressive therapy until the lymphoma has been treated and the patient is in remission. At that point, the gastroenterologist should have a conversation with the patient and his or her oncologist, at which time they can make decisions about what, if any, therapies should be used the next time the patient experiences an IBD relapse. If the patient has ulcerative colitis, surgical therapy may become a more attractive option when there are concerns about lymphoma. In contrast, surgery is not a long-term solution for most patients with Crohn's disease, so these individuals will likely require additional medical therapies; in these cases, the clinician must select among the various medications available and try to balance potential benefit versus potential harm.

G&H Aside from surgery, what other alternatives might be considered for these patients?

JDL The risk of lymphoma and other cancers is thought to be lower with methotrexate than with thiopurines (and may also be lower with methotrexate than with anti-TNF drugs), so methotrexate may be preferred in Crohn's disease patients who have a history of lymphoma. Also, some patients can be managed with an intermittent course of steroids. Finally, several new IBD therapies will likely become available within the next decade, and hopefully 1 or 2 of these new therapies will allow for less systemic immunosuppression, which

would make these treatments better options for patients who are at higher risk for lymphoma.

G&H What further research is needed regarding management of lymphoma in IBD patients?

JDL We need more data about how and when we can use immunosuppressants to treat patients who have a history of cancer—whether it is lymphoma, leukemia, or a solid cancer. We know that survivors of childhood cancers, including lymphoma, have a higher incidence of second cancers, and they also have a higher incidence of other diseases, including gastrointestinal diseases. As treatment for cancer gets better and more patients survive, clinicians will need to know how best to treat cancer survivors who have long-term systemic illnesses such as IBD, rheumatoid arthritis, psoriasis, or multiple sclerosis. Currently, immunosuppressant therapies are the mainstay of therapy for these diseases, which poses a dilemma for patients who are at risk for cancer.

Suggested Reading

Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut*. 2005;54:1121-1125.

Bewtra M, Lewis JD. Safety profile of IBD: lymphoma risks. *Gastroenterol Clin North Am*. 2009;38:669-689.

Beaugerie L, Brousse N, Bouvier AM, et al; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374:1617-1625.

Herrinton LJ, Liu L, Weng X, Lewis JD, Hutfless S, Allison JE. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. *Am J Gastroenterol*. 2011;106:2146-2153.

Van Assche G, Lewis JD, Lichtenstein GR, et al. The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organisation: safety. *Am J Gastroenterol*. 2011;106:1594-1602; quiz 1593, 1603.