Inflammatory Bowel Disease and Lymphoma: A Comprehensive Review for the General Gastroenterologist

INTRODUCTION

Idiopathic Inflammatory Bowel Disease (IBD) is generally divided into Crohn’s disease (CD) and Ulcerative Colitis (UC). Management of both CD and UC has traditionally focused on improving the signs and symptoms of intestinal involvement. Newer and more aggressive therapies are targeted to mucosal healing, decreased rates of surgery and other complications.

There has long been concern that IBD itself or the treatments used in the management of IBD may predispose patients to the development of lymphoma. Though lymphoma is rare, single center reviews up to population wide investigations have attempted to define the relationship between lymphoma and IBD. Albeit inconsistent, the general consensus is that IBD itself is not associated with an increased risk of lymphoma, but treatment with the thiopurines 6-mercaptopurine (6-MP) or azathioprine (AZA), and possibly biologic therapies, may be. We have provided a brief review of the more recent evidence on this important topic.

Lymphoma Risk and Crohn’s Disease

Currently, the risk of lymphoma adjusted for age is believed to be 22.5 per 100,000 for both men and women. The rate for men is notably higher than that for women, at 27 to per 100,000 as compared to 18.8-100,000 per the Surveillance Epidemiology and End Results (SEER) database 2005-2009. Before addressing the possible role of IBD therapies in the development of lymphoma it is important to establish whether IBD itself poses an increased risk. This relationship has already been identified for other chronic inflammatory conditions such as rheumatoid arthritis, with increased rates of lymphoma noted, especially in those with more active disease.1,2

Referral institutions and population level studies have attempted to define the risk of lymphoma for individuals with IBD. The population based studies are especially helpful since they include patients across all spectrum of disease severity and medication usage. Conversely, studies addressing rates of lymphoma from tertiary care populations tend to include patients with
a greater disease severity and more frequent use of immunosuppressive and modifying therapies, possibly biasing their observations.

A recent single center study from Spain reviewed the records of 911 IBD patients and found a higher than expected rate of lymphoma, 7 patients in all. Five of these patients however had been treated with thiopurines, and 4 patients had also received biologic therapy. An earlier study of hospitalized CD patients from the United States showed an increased odds ratio adjusted for age, gender, and race of lymphoma in CD of 2.04 (95% CI 1.33-3.14). Yet a recent Indiana University School of Medicine study provided data on 3585 IBD patients with an average of 8.4 years of observation. Of these patients 2,277 had CD. A total of 8 lymphoma cases were confirmed, of which 5 of these had CD. Overall, no statistically significant increased risk of lymphoma was observed.5

Population based studies, by their nature, examine a much broader array of patients, treatments, and degrees of disease severity. The recent Dutch National Database of PALGA reviewed patients with IBD who developed lymphoma between the years of 1997 and 2004. A cohort of 17,834 IBD patients were identified, with 44 observed lymphomas. 34% of these cases (15/44) were in patients with CD. The overall relative risk was calculated at 1.27, (95% confidence interval 0.92-1.68). Though the study did not provide risk analysis based on IBD subtype, it did examine variables such as age and gender. A significant increased risk of lymphoma was noted in males, in the age group 35-39 years. RR 10.25 (95% CI 2.56-23.05) 6

A recent Swedish cancer registry study identified 21,788 CD patients hospitalized during the years 1964-2004. 1424 cancers were identified. There was a higher observed incidence of non-Hodgkin’s lymphoma in these patients (Standardized Incidence Ratio, SIR 2.54, range 2.03-3.15), particularly within one year of the diagnosis of CD. This effect was markedly decreased in those with a longer history of CD. The study also reported significantly higher rates of small intestinal malignancy along with colon liver, kidney and testis cancer. The Manitoba Canada group examined 21,340 person years of CD. An increased relative risk of lymphoma was observed for males only. (3.63; 95% CI 1.53-8.62). No increased risk was noted for those patients with UC (19,665 person-years) In contrast, results from the general practice research database of 6605 patients with CD did not show a significant increased relative risk of lymphoma (RR= 1.20; 95% CI, 0.67-2.06). There was also no increased risk of lymphoma in those patients with UC, RR= 1.11 (95% CI, 0.51-2.19).9

The largest population based study examined 47,679 Swedish patients with IBD, including subjects between the years of 1955 and 1990 from regional cohorts (N=8,028), and from the Inpatient Register of 1964-2000, (N=45,060) 10 In CD patients a borderline significant increased lymphoma risk was noted, (SIR 1.32; 95%CI 1.0-1.7), but only for the inpatient cohort. Again, there was an increased risk for men with CD, (SIR 1.5; 95%CI 1.1-2.0) which was not observed for women or with UC. Several smaller studies have shown similar results.11-15

Two recent meta- analyses are of value. von Roon et al. examined over 60,000 patients with Crohn’s disease from 34 studies, showing a very mild but statistically significant increased risk in the development of lymphoma for patients with CD.16 Relative risk 1.42 (95% confidence interval 1.16-1.73). Their meta-analysis combined studies that were both population based as well as those from single referral centers. Another meta-analysis by Pedersen et al included all IBD patients, but limited inclusion to population based studies.17 Eight studies were identified totaling 17,052 patients with IBD. Overall, there was no observed increased incidence of extra-intestinal cancers. An increased risk of lymphoma did not reach statistical significance, with a SIR of 1.42(CI 0.95-2.12).

**Thiopurines and Lymphoma**

Even with the advent of newer biologic therapies, the thiopurines (AZA and 6MP) remain a mainstay of IBD management. Thiopurine use has clearly been associated with an increased risk of lymphoma in patients with rheumatoid arthritis, as well as those on post transplant immunosuppression.18, 19 In many the mechanism is believed to involve either reactivation, or de novo infections with the Epstein Barr virus.20 An increased risk of lymphoma in one population however does not automatically translate to another.

Early single center studies showed a wide range of results, from no significantly increased risk of lymphoma with thiopurines, to those with standardized incidence ratios (SIRs) as high as 37.5. A meta-analysis of five of these earlier studies and a single population based study was performed by Kandiel et al.9, 21-26
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In total, 11 lymphomas were observed among 3,891 patients treated with either AZA or 6MP. The rate of observed lymphomas was compared with the expected rate of 2.63 lymphomas derived from the Surveillance Epidemiology and End Results (SEER) cancer registry. The analysis showed that there was an increased risk of lymphoma associated with AZA and 6MP use, with a pooled relative risk of 4.18 (95% confidence interval 2.07-7.51) The majority of the lymphoma cases were men, with a median of 14 months of therapy. Of note, the temporal relationship of thiopurine use and lymphoma was not described and there remained the concern of possible bias, with so many of the subjects coming from tertiary referral centers.

More recently, further insight has come from the publication of the large nationwide prospective population based study from France, CESAME.27 The study tracked 19,486 patients with IBD, 60.3% of which had CD over a 3 year period. Patients were recruited between May of 2004 and June of 2005. Follow-up ended December 31, 2007. At enrollment 5867 patients were receiving a thiopurine, 2809 had discontinued, and 10,810 had never received thiopurines. Over the follow-up there were 22 new cases of non-Hodgkin lymphoma. The study found an increased risk of lymphoproliferative disorders for those patients receiving thiopurines as compared to those who had never received thiopurines, hazard ratio 5.28 (2.01-13.9, P = 0.0007). Notably there was no increased risk of lymphoma among those patients with previous thiopurine use who had discontinued their therapy. There was also no increased risk of lymphoma in those patients who had never received a thiopurine as compared to the general population.

Since the publication of CESAME, another population based study, this one retrospective, of 15,471 IBD patients from the UK showed a similar increased risk of lymphoma, odds ratio of 3.22, (CI=1.01-10.18).28 A lower, but still significantly increased risk of lymphoma with thiopurine use has been noted among patients followed by the Kaiser Permanente IBD Registry.29

While AZA and 6MP use is more common, methotrexate is also used as an immune suppressing treatment for Crohn’s disease. Though single center, tertiary care data suggesting an increased risk of lymphoma with its use exists,24 there has been little published on the matter of lymphoma risk in IBD.

Biologic Therapy and Lymphoma

Currently, infliximab is subject to an FDA boxed warning regarding an increased risk for lymphoma. Specifically, it states “Lymphoma and other malignancies have been reported in children and adolescent patients receiving TNF-blocking agents including infliximab” though this association has only been seen with rheumatoid arthritis. A similar warning is also given for adalimumb and certulizumab pegol, but not natalizimab.

Currently, there is limited data available specifically addressing the risk of lymphoma with biologic monotherapy for IBD. Results from the Crohn’s Therapy Resource, Evaluation and Assessment Tool (TREAT) Registry from 2006, and an update in 2008 addresses this issue. The report included 6273 patients with 24,575 patient years of follow-up. Among this group of IBD patients 3396 patients had received infliximab, with 14,184 patient years of follow-up. Mean follow-up was 4.1 years. Infliximab treated patients had more severe disease than the non infliximab treated patients, and were more likely to be on immunomodulators,(49.0% versus 31.7%), yet there was no increase in the incidence of lymphoma in the infliximab group.30

That same year, a meta-analysis analyzed 21 placebo controlled trials of a variety of anti-TNF agents for treatment of CD. 5356 patients were included, of which 3341 received infliximab, adalimumab, certolizumab, CDP571, etanercept, oronorcept, and the other 2015 received placebo. Median follow-up was 24 weeks, with a range of 4-60 weeks. No details were provided regarding concurrent or past use of thiopurines. No significant difference was detected in the frequency of malignancies between anti-TNF (n=8) and controls (n=8)(0.24% versus 0.39%, respectively, 95% CI, -0.45-0.18).31

Another meta-analysis of 26 studies included randomized controlled trials, cohort studies, and case series of anti-TNF therapy for adult CD patients.32 A total of 8905 patient’s with 21,178 patient years of follow-up were included. The minimum median follow-up for the included studies was 48 weeks. The expected rate of non-Hodgkin lymphoma was derived from the SEER cancer registry and the prior meta-analysis of patients treated with 6-MP or AZA performed by Kandiel et al.

Overall, 13 lymphomas were observed in 21,178 patient years of follow-up, for a rate of 6.1 of NHLs per 10,000 patient years. When compared to the expected rate in all age groups in SEER (1.9 per 10,000
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Combination Therapy

Recent concern has also been raised regarding the lymphoma risk of combined biologic and immune modifying therapy. Understanding of this risk is especially relevant, considering the accumulating Evidence supporting early combined therapy for CD such as the recent SONIC study has placed additional pressure on treating physicians to alter their practice from traditional sequential step up therapy to more aggressive early combination therapy.

While the Siegel meta-analysis did not show any increased risk of lymphoma overall with combination therapy compared to thiopurine monotherapy, another report from the Kaiser Permanente IBD and Cancer Registries of 16,023 IBD patients had an average 5.8 years of follow up and identified 43 lymphomas. Overall the authors were able to analyze 21,282 person years of exposure to thiopurine alone 81%, anti-TNF alone 3%, and the combination 16%. They observed a significantly increased risk of lymphoma among patients treated with thiopurine alone, SIRR 1.4 (95% CI: 1.2-2.7). For anti-TNF with past use of thiopurine, the SIRR was 5.5 (95% CI: 4.5-6.6) and for anti-TNF and current use of thiopurine the SIRR was 4.4 (95% CI: 3.4-5.4). While the SIRRs for combined therapy are larger than for thiopurine monotherapy, this does not prove an increased risk of combined therapy over thiopurine monotherapy.

The aggressive lymphoma variant, hepato-splenic T-cell lymphoma (HSTCL) was first described in a CD patient treated with thiopurine monotherapy. The publication of the first case report of HSTCL with combination therapy in 2005 raised additional concerns. Since that initial case report, enough additional cases have accumulated to warrant a specific black boxed warning for infliximab; “Hepatosplenic T-cell lymphoma has been reported in patients with Crohn’s disease or ulcerative colitis treated with infliximab and concurrent or prior azathioprine or mercaptopurine use, usually reported in adolescent and young adult males.” The warning also applies to adalimumab. Though it’s uncertain whether IBD patients who developed lymphoma have a prognosis that differs from non-IBD lymphoma patients, what is certain is the aggressive and almost universally fatal course of HSTCL.

A recent systematic review of available case reports of IBD and lymphoma provides a comprehensive update of 36 patients found to have developed HSTCL with treatment for IBD since 1996. The median patient age was 22.5 years. Of the 31 patients for whom gender information was available, only two were female (6.5%) and 26 (72%) had CD. Of these 36 patient’s, 20 were receiving combination therapy with either AZA or 6-MP and anti-TNF therapy (15 with infliximab, 4 with infliximab followed by adalimumab, and 1 with infliximab, adalimumab and natalizumab). The 16 remaining cases occurred in patients receiving thiopurine monotherapy. Notably, there were no cases of HSTCL found for patients who received anti-TNF therapy alone.

The authors point out that while only 38 cases of HSTCL were reported by the National Cancer Institute SEER database between the years 2001 and 2007, at least 16 of these had IBD, suggesting an increased risk of HSTCL in the IBD population. The results of their survey also suggested a stronger association with the use of thiopurines either as mono-therapy or in combination with biologic. Notably, the median duration of therapy with thiopurine was 5.5 years in the combined therapy group and 6.0 years in the monotherapy group, suggesting an increased risk with longer durations of therapy. Only one patient used a thiopurine for less than 2 years. Overall, the authors emphasize a risk of 1:3534 in male patients under the age of 35 years.

Summary and Recommendations

Among the challenges of treating the patient with IBD, the issue of lymphoma remains a major concern. The absolute risk of lymphoma for IBD patients remains small, and is likely not increased over those in the general population. Though treatment with thiopurines, biologic therapies, or a combination of the two increases the relative risk of lymphoma, the
absolute risk remains small. However, even a small increased risk of malignancy is a major concern to the patient, and can radically alter their attitude and choice of therapy. The challenge remains to recommend and initiate appropriate therapy at an appropriate time. Generally, the risks of morbidity and mortality related to IBD itself are far greater than the risk of treatment related lymphoma.\(^{39, 40}\) Only by having a full command of the available information on this topic can we truly help our patients to make an informed decision.  

References


