Lymphoma Risk in Inflammatory Bowel Disease: Role of Azathioprine/6-Mercaptopurine and Infliximab

by Wojciech Blonski*, Rabi Kundu and Gary R. Lichtenstein

There has been controversy regarding the prevalence of lymphoma in patients with inflammatory bowel disease (IBD) i.e. Crohn’s disease or ulcerative colitis. Tertiary center studies have reported the increased risk of lymphoma in patients with IBD whereas the majority of population based studies did not find such a risk when compared to the general population. Azathioprine/6-mercaptopurine and infliximab are immunomodulatory agents used in the treatment of IBD. This review discusses the relationship between IBD, treatment of IBD (with azathioprine/6-mercaptopurine and infliximab) and the risk of lymphoma.

INFLAMMATORY BOWEL DISEASE AND RISK OF LYMPHOMA

There has been controversy regarding the prevalence of lymphoma in patients with inflammatory bowel disease (IBD) i.e. Crohn’s disease or ulcerative colitis. Studies from tertiary medical centers showed the increased risk of lymphoma in IBD patients than in population based studies. This fact might be explained by the possibility of increased risk of lymphoma only in patients with severe IBD who are usually referred to tertiary medical centers. In addition, such patients usually have failed various different medical therapies and may have used a variety of immunosuppressive drugs which in themselves may have potential for developing lymphoma.

There have been five retrospective studies performed in tertiary medical centers to date suggesting an increased incidence of lymphoma in patients with IBD. In two studies it was suggested that inflammatory bowel disease itself was a predisposing factor for development of lymphoma (1,2). The first study demonstrated a relative risk of 6.12 for non-Hodgkin’s and 3.41 for Hodgkin’s lymphoma in 1,961 patients with IBD (1). Similarly, Masel, et al in their analysis showed an increased incidence of non-Hodgkin’s lymphoma in patients with IBD (5 non-Hodgkin lymphomas among 4,791 IBD patients) (2). Moreover, another analysis of 1,248 patients with ulcerative colitis from a tertiary medical center found the significantly increased risk ratio of 3.41 for developing lymphoma in IBD (3). Furthermore, a study of 2,636 IBD

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patients also suggested association between IBD and lymphoma which occurred in 9 patients who were not treated with antimetabolites (5 of them also did not receive sulfasalazine or steroids before the diagnosis of lymphoma) (4). In addition, another tertiary medical center reported an increased 2-year cumulative incidence of lymphoid/myeloid malignancies among 5,426 hospitalized patients with Crohn’s disease compared to those without Crohn’s disease (21 subjects with lymphoid/myeloid malignancies, RR 2.04, p < 0.001) (5). Data from the aforementioned studies are presented in Table 1.

In contradistinctions to the aforementioned studies there have been three retrospective and hospital-based studies which did not find an increased risk of lymphoma in 8,704 patients with IBD (3,158 with Crohn’s disease and 5546 with ulcerative colitis) (6–8) (Table 1). Additionally there have been five population-based studies which did not find an increased risk of lymphoma in patients with IBD relative to the general population (9). The authors established the relative risk of lymphoma for patients with IBD as compared to their 60,506 matched controls of 1.20 (9). The relative risk (RR) of lymphoma was similar in both patients with Crohn’s disease (n = 6,605, RR = 1.39) and ulcerative colitis (n = 10,391, RR = 1.11). It should be noted that the characteristics of patients with IBD and lymphoma were generally similar to the patients with IBD without lymphoma (9). Therefore, neither Crohn’s disease nor ulcerative colitis were associated with disease related increased risk of developing lymphoma (9). Although the authors did not observe the evidence that therapy with azathioprine or 6-mercaptopurine increased risk of lymphoma, they could not preclude the possibility of increased risk of lymphoma in patients treated with immunomodulators given the small number of such patients evaluated (9).

Four previous population-based studies including 8,028 patients, also did not find an increased relative risk of lymphoma in patients with IBD compared with the general population (10–12) (Table 1). Ebbkom, et al reported 1.0 risk ratio (RR) of lymphoma among 4,776 patients with IBD (RR = 0.4 for 1,655 patients with Crohn’s disease, RR = 1.2 for 3,121 patients with ulcerative colitis) (10). Two further studies found the 1.35 and 1.2 risk ratios of lymphoma in 1,251 patients with Crohn’s disease and 1,547 patients with ulcerative colitis, respectively (11,12). Finally, population-based study from Minnesota found the 1.0 risk ratio in 454 patients with IBD (RR = 0 for 238 UC, RR = 2.4 (ns) for 216 CD) (13).

However two other population based studies, including 6,449 patients, reported elevated risk of certain types of lymphomas in certain patients with IBD (14,15) (Table 1). One study (n = 920) reported a strongly increased significant 9-fold risk of Hodgkin’s lymphoma in 689 patients with ulcerative colitis (14) and non-significant increase in 231 patients with Crohn’s disease. In addition, the authors found non-significant 2-fold excess risk for non-Hodgkin lymphomas in patients with ulcerative colitis (14). The second, study (n = 5,529) reported a significantly increased risk of developing lymphoma only in male patients (3.63) (15). The risk of lymphoma in patients with ulcerative colitis and female patients with Crohn’s disease was not significantly increased (1.03, 1.09 respectively) (15).

AZATHIOPRINE/6-MERCAPTOPURINE IN IBD AND RISK OF LYMPHOMA

The immunomodulatory agents, azathioprine and 6-mercaptopurine, are frequently used in patients with inflammatory bowel disease for induction of remission in moderate to severe disease, for maintenance of remission, for steroid sparing and for treatment of fistulizing Crohn’s disease (16). Both agents are inactive prodrugs belonging to thiopurine analogues (16). After administration, azathioprine, which is nitroimidazole derivative of 6-mercaptopurine, is cleaved rapidly to 6-mercaptopurine and imidazole derivative within the erythrocytes (16). The active metabolites (6-thioguanine nucleotides) interfere with DNA and RNA synthesis and chromosomal replications acting as purine antagonists (16). The active metabolites (6-thioguanine nucleotides) interfere with DNA and RNA synthesis and chromosomal replications acting as purine antagonists (16). These agents also cause inhibition of lymphocytes B and T proliferation, interference with natural killer cells cytotoxicity, decrease suppressor T-cell function and cell mediated immunity as well as induce T-cell apoptosis (16).

Azathioprine and 6-mercaptopurine have been associated with an increased risk of lymphoma, especially non-Hodgkin lymphoma in patients with rheumatoid arthritis or subjected to organ transplantation (17–23).
This raised concern about the possibility of development of lymphomas in patients with IBD treated with these agents, which prompted several studies evaluating the safety of these agents in patients with IBD.

There were a total of five studies performed in tertiary medical centers which evaluated the risk of malignancies in patients with IBD who were treated with azathioprine or 6-mercaptopurine (24–28) (Table 2). There were 3 cases of lymphoma reported among 946 patients treated with 6-mercaptopurine (0.3%) (24,25), no lymphomas among 755 treated with azathioprine (0

### Table 1. Studies evaluating the risk of lymphoma in patients with IBD.

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients</th>
<th>Design</th>
<th>Prevalence of Lymphoma</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenstein et al 1985</td>
<td>1961</td>
<td>hospital-based</td>
<td>-6 NHL: RR: 6.12 (p&lt;0.005)</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>734</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1227</td>
<td></td>
<td>-2 HL: RR: 3.41 (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Gyde et al 1980</td>
<td>513</td>
<td>hospital-based</td>
<td>0 lymphomas: RR: 3.41 (p=0.06)</td>
<td>X</td>
</tr>
<tr>
<td>Masel et al 2000</td>
<td>4791</td>
<td>hospital-based</td>
<td>5 NHL</td>
<td>X</td>
</tr>
<tr>
<td>Mir-Madjlessi et al</td>
<td>1248</td>
<td>hospital-based</td>
<td>-3 lymphomas: RR: 3.41 (p=0.06)</td>
<td>X</td>
</tr>
<tr>
<td>Greenstein et al 1992</td>
<td>2636</td>
<td>hospital-based</td>
<td>-9 lymphomas (5 UC, 4 CD)</td>
<td>X</td>
</tr>
<tr>
<td>Arseneau et al 2001</td>
<td>5426</td>
<td>hospital-based</td>
<td>-21 lymphoid/myeloid malignancies: RR 2.04 (p&lt;0.001)</td>
<td>X</td>
</tr>
<tr>
<td>Mellemkjaer et al 1995</td>
<td>5546</td>
<td>hospital-based</td>
<td>-6 NHL (RR: 1.4)</td>
<td>X</td>
</tr>
<tr>
<td>Mellemkjaer et al 2000</td>
<td>2645</td>
<td>hospital-based</td>
<td>-1 HL (RR: 1.0)</td>
<td></td>
</tr>
<tr>
<td>Loftus et al 2000</td>
<td>454</td>
<td>population-based</td>
<td>1 NHL (RR: 1.0)</td>
<td>X</td>
</tr>
<tr>
<td>Ekbom et al 1991</td>
<td>4776</td>
<td>population-based</td>
<td>9 lymphomas (8 UC, 1 CD): RR: 1.0 (1.2 UC, 0.4 CD)</td>
<td>X</td>
</tr>
<tr>
<td>Persson et al 1994</td>
<td>1251</td>
<td>population-based</td>
<td>4 lymphomas (RR:1.35)</td>
<td>X</td>
</tr>
<tr>
<td>Karlen et al 1999</td>
<td>1547</td>
<td>population-based</td>
<td>3 lymphomas (RR: 1.2)</td>
<td>X</td>
</tr>
<tr>
<td>Palli et al 2000</td>
<td>920</td>
<td>population-based</td>
<td>IBD: 5 HL (RR 8.62): 2 NHL (RR:1.43)(ns) UC: -4 HL (RR:9.3), 2 NHL (RR:1.8 ns) CD: -1 HL (RR:2.5 ns), 0 NHL</td>
<td>X for HL in UC</td>
</tr>
<tr>
<td>Bernstein et al 2001</td>
<td>5529</td>
<td>population-based</td>
<td>16 lymphomas (7UC; RR 1.03,9CD, RR 2.40)</td>
<td>X for CD</td>
</tr>
</tbody>
</table>

Lymphoma Risk in IBD

observed vs. 0.52 expected from the general population) (26) and 1 lymphoma among 157 patients treated with azathioprine or 6-mercaptopurine (27). Finally, the recent study evaluating 626 azathioprine- treated patients reported 3 lymphomas (0.5%) also did not show any risk of lymphoma with treatment (28). Furthermore, it has been suggested in decision analysis model that benefits from azathioprine therapy outweigh the risk of lymphoma (29). Therapy with this agent to prolong remission in patients with IBD increased quality-adjusted life expectancy for most patients (29).

The only one population-based study which evaluated the risk of lymphoma in 1,465 patients treated with azathioprine/6-mercaptopurine did not find a significantly increased risk of lymphoma with the relative risk of 1.27 compared to patients with IBD not treated with these agents (9) (Table 2).

On the other hand, three studies have demonstrated an increased risk of lymphoma in IBD patients treated with azathioprine/6-mercaptopurine (30–32) (Table 2). The significantly increased risk (59 times) of non-Hodgkin lymphoma (NHL) compared with that expected in the general population (p = 0.001) was demonstrated in the group of 238 patients with IBD treated with immunosuppressants (azathioprine, methotrexate or cyclosporin) (30). There were 4 cases of NHL among 238 patients (1.7%) on immunosuppressants (2 in azathioprine treated patients) and 0 cases of NHL in 544 patients with IBD without immunosuppressive treatment (30). Furthermore, Lewis, et al have demonstrated in their meta-analysis of six previous studies a significant 4-fold increase in the risk of lymphoma in patients with IBD treated with azathioprine/6-mercaptopurine (31).

Moreover, the relationship between treatment of IBD with azathioprine or 6-mercaptopurine and Epstein-Barr virus (EBV) positive lymphoma has been evaluated in one study and several case reports. Dayharsh, et al observed in their retrospective study a significant association (p = 0.013) between EBV positive lymphoma and prior treatment with azathioprine or 6-mercaptopurine (32). Among 1,200 patients with IBD treated with these agents for median 3.5 years, 5 patients developed EBV-positive lymphoma and 1 EBV-negative lymphoma (32). Only 2 patients with IBD developed EBV-positive lymphoma without a history of treatment with azathioprine/6-mercaptopurine (32). Therefore, treatment with these agents may be associated with a small increased risk of EBV-positive lymphoma (32). Furthermore, several case reports suggest the potential for the small increased risk of Epstein-Barr virus positive lymphoma in patients with IBD treated with these agents (33–36).

INFLIXIMAB IN IBD AND THE RISK OF LYMPHOMA

Infliximab is a chimeric, mouse-human (approximately 25% mouse and 75% human origin), monoclonal anti-TNF-α antibody of approximate molecular weight of 149,1000 Daltons, in which the entire variable domain derived from a murine anti-TNF-α hybridoma is attached to a human IgG1 constant region derived from plasmid expression vectors (37-40). The variable region of this antibody specifically binds to TNF-α with high affinity and specificity while the constant region mediates its effector functions including antibody-dependent cellular toxicity, complement fixation and antibody clearance (37-39). In vitro, infliximab binds both soluble and transmembrane forms of TNF-α and mediates antibody-dependent and complement-dependent cytotoxicity on cells with high levels of TNF-α expression (41). The IgG1 portion of the antibody causes apoptosis of T lymphocytes (42).

Infliximab was approved by the FDA in the US in 1998, and is indicated for the treatment of moderate to severely active Crohn’s disease unresponsive to conventional therapy such as aminosalicylates, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine or methotrexate or fistulizing Crohn’s disease in order to reduce the number of draining enterocutaneous and rectovaginal fistulas and to maintain their closure (43,44). However, its use in ulcerative colitis still remains off labeled indication (45).

Infliximab is also indicated in patients with moderately to severely active rheumatoid arthritis (RA) with inadequate response to methotrexate (46). It should be stressed that unlike patients with IBD those with RA have been found to have an increased risk of lymphoma (average RR = 2) compared to the general population (47–50), especially in patients with high inflammatory activity of this disease (51). Although the large study (n = 18,572) by Wolfe, et al observed significantly
higher risk of lymphoma in RA patients treated with infliximab than methotrexate (2.6 vs.1.7), the authors claimed that it might have been due to the fact that patients with the highest risk of lymphoma (with high inflammatory activity of RA) received anti-TNF therapy (50). Randomized placebo controlled ATTRACT trial including patients with rheumatoid arthritis treated with infliximab reported 1 lymphoma (B-cell) among 342 patients exposed to infliximab (0.3%) and none in placebo treated patients (52). The same study reported 3 other lymphomas among 555 RA patients (0.55%) treated with infliximab in not specified six other clinical trials (52). Current data from clinical trials and from other studies is not sufficient enough to establish a causal relationship between infliximab treatment and the development of lymphoma (50).

Because of the increased rate of lymphoproliferative disorders in immunosuppressed or immunodeficient patients (53), it is appropriate to attempt to discern if there is an association between treatment with immunomodulating agent, treatment with infliximab and the risk of developing lymphoma in patients with IBD. At this time, the trial and postmarketing experience data do not indicate an increased risk of development of lymphoma in patients with IBD treated with infliximab (54). However, vigilance is indicated as the duration of follow-up of patients with IBD treated with infliximab is short (55) and additional caution should be considered when recommending infliximab in patients with history of malignancy (55).

Data from the three randomized placebo controlled clinical trials using infliximab in CD (n = 952) documented 2 cases of lymphoma (0.2%) in patients with infliximab exposure (56–58). Among those reported lymphomas there was 1 natural-killer-cell lymphoma in a patient on placebo maintenance (10 months after the last infusion of placebo; the patient received a single infusion of 5 mg/kg infliximab at the beginning of the trial) (56) and 1 case of intravascular duodenal B-cell lymphoma in 1 placebo retreated patient 9.5 months after initial infusion of infliximab (58). Two additional cases of both non-Hodgkin lymphoma and Hodgkin lymphoma in patients on concomitant treatment with azathioprine (0.4%) were reported in a retrospective safety analysis including 500 patients with CD

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(59). Furthermore, a recent population based cohort study from Sweden found 3 lymphomas (1 natural killer cell and 2 B cell lymphomas) in 217 patients with IBD (1.4%) treated with infliximab (60). In addition, the TREAT registry studying long-term safety of infliximab in CD, following prospectively over 5,000 patients with Crohn’s disease reported a similar prevalence of lymphomas in patients treated with infliximab and those on other treatment. (55,61). According to the manufacturer there were 4 lymphomas among 6,417 infliximab treated patients and 3 lymphomas among 5,225 patients with other treatment in the TREAT registry (55). Thus, the number of patients who developed lymphoma after exposure on infliximab has not so far exceeded the range reported in patients who developed lymphomas because of their disease (55). As of February 2003, postmarketing surveillance has documented 71 cases (45 in RA, 20 in CD) of lymphoma among 365,000 patients treated with infliximab (54). In addition a recent case report reported a patient with Crohn’s disease treated with azathioprine and a single infusion of infliximab who developed EBV-positive B cell ileal lymphoma (62). It demonstrates that awareness of the possibility of lymphoma in patients treated with infliximab especially with additional immunomodulators should be maintained.

SUMMARY

Current data from population-based studies strongly suggest that inflammatory bowel disease is not a pre-disposing factor for the development of lymphoma and the risk of lymphoma is not significantly increased when compared to the general population. Although the existing data do not indicate that there is a significantly increased incidence of lymphoma in patients with IBD treated with azathioprine/mercaptopurine or infliximab, it is premature to definitely exclude the potential association between treatment with these agents and the development of lymphoma. It should be stressed that continued vigilance is recommended in these patients during therapy as the duration of follow up remains somewhat limited. Further prospective, population based studies with long term follow-up are required to fully evaluate the risk of lymphoma in patients with IBD treated with azathioprine/6-mercaptopurine or infliximab.

References

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