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The risk of lymphoma and immunomodulators in patients with inflammatory bowel diseases: Results from a population-based cohort in Eastern Europe

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Abstract

Background and aims: Prior studies suggest a small but significantly increased risk of lymphoma in adults with inflammatory bowel disease (IBD), especially in patients treated with thiopurines. No data was available from Eastern Europe. The aim of this study was to analyze the incidence of lymphomas as related to drug exposure, in a population-based Veszprem province database, which included incident cases diagnosed between January 1, 1977 and December 31, 2008.
Methods: Data from 1420 incident patients were analyzed (UC: 914, age at diagnosis: 36.5 years; CD: 506, age at diagnosis: 28.5.5 years). Both in- and outpatient records were collected and comprehensively reviewed. The rate of lymphoma was calculated as patient-years of exposure per medication class, of medications utilized in IBD.

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Results: Of the 1420 patients, we identified three patients who developed lymphoma (one CLL, two low-grade B-cell NHL including one rectal case), during 19,293 patient-years of follow-up (median follow-up: 13 years). All three patients were male. None had received azathioprine or biologicals. The absolute incidence rate of lymphoma was 1.55 per 10,000 patient-years, with 3 cases observed vs. 2.18 expected, with a standardized incidence ratio (SIR) of 1.37 (95% confidence interval [CI]: 0.44–4.26). No cases have been exposed to either azathioprine or biologicals.

Conclusions: The overall risk of lymphoma in IBD was not increased; only three cases were seen in this population-based incident cohort over a 30-year period. An association with thiopurine exposure was not found.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders with increasing incidence and prevalence. CD may involve any part of gastrointestinal tract, and is characterized by ulcerations and transmural inflammation that may produce complications, including bowel strictures or fistulas; whereas in UC the inflammatory process is restricted to the colon.[1,2] Current therapeutic modalities have changed significantly over the last decades, with more widespread and earlier use of biologicals and immunomodulator agents (e.g. azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]). There exists increasing evidence that the change in treatment is associated with a change in the natural history of the disease.[3] In contrast, available evidence may suggest a possible link between IBD, immunomodulator therapy and tumor risk, including risk for colorectal cancer[4,5] and lymphoma.

The incidence of malignant lymphomas has increased recently worldwide in recent years. In the United States, NHL now represents the fifth most commonly occurring cancer, with an incidence of 19 per 100,000 people annually. NHL appears more often in Caucasians than in Afro-Caribbeans, and affects males more frequently.[6] Lymphomas that develop in IBD are heterogeneous. Generally, lymphomas can be divided into non-Hodgkin's lymphoma (90% of lymphomas) and Hodgkin's lymphoma (10% of lymphomas). The risk of lymphoma in IBD patients may be associated with two main factors: the inflammatory process itself and the widespread use of immunomodulators for prolonged periods. Inflammation has been reported as a risk factor for neoplasm in patients with RA.[7,8] In a Swedish RA cohort, authors detected a 70-fold increase in lymphoma risk in patients with high disease activity, suggesting that the disease activity itself, rather than the therapy, can be a risk factor for lymphomatous transformation. The same was reported also in IBD.[9] Nonetheless, it has been shown that immunomodulators can increase the risk of lymphoma in AIDS and transplantation recipients[10] as well. Some therapeutic modalities, such as alkylating agents and MTX, are risk factors of lymphoma in RA, but only a fraction of lymphomas can be attributed to the carcinogenic effects of these drugs. Similar considerations should be applied for cyclophosphamide, chlorambucil, AZA, and other conventional immunomodulator medications.

In most population based studies IBD itself does not appear to be associated with an increased risk of lymphoma.[11–15] In one of the early reports by Lewis et al.,[11] the incidence of lymphoma was not elevated in CD (RR: 1.39) or UC (RR: 1.11), as compared to controls. In contrast, Bernstein et al.[16] reported that incidence rates and rate ratios of lymphoma were increased for males with CD only (3.63; 95% CI: 1.53–8.62). A potential deleterious role for immunosupressives was also suggested by the meta-analysis by Kandiel et al.,[17] where the pooled relative risk of lymphoma in CD patients treated with immunomodulators (AZA or MTX) was 4.18 (95% CI: 2.47–7.51). Increased risk of lymphoma was thought to be due to medication, disease severity, or a combination of the two. In addition, the risk of lymphoma was reported to be increased in the CESAME study.[18] At baseline, 30.1% of patients had current immunomodulator therapy, while 10.0% had discontinued immunosuppressants, and 55.5% were immunosuppressant-naïve. One case of Hodgkin disease and 22 cases of NHL were reported. The multivariate-adjusted hazard ratio of lymphoproliferative disorders in patients receiving thiopurines versus those who had never received the drugs was 5.28 (2.01–13.9, $p=0.0007$). The same researchers reported recently that the risk for primary intestinal lymphoproliferative disorders was increased in patients with IBD.[19] The reported standardized incidence ratio was 17.5 (95% CI: 6.4–38.1) and risk was highest in patients exposed to thiopruines (SIR: 49.4; 95% CI: 13.5–126.8).

In contrast, there are no published studies that rigorously investigated the risk of lymphoma in IBD patients treated with MTX. The potential association was examined indirectly in the hospital-based study by Farrell et al.,[20] where 2 of 31 MTX exposed patients developed NHL. Of note, one of these patients who developed NHL was also exposed to cyclosporine. Finally, in a meta-analysis by Siegel et al. the risk of lymphoma was reported to be increased in patients with previous immunomodulator exposure who were currently receiving anti-TNF agents (SIR: 3.23, 95% CI: 1.5–6.9).[21]

Since previous studies suggest a small but significantly increased risk of lymphoma in adults with inflammatory bowel disease (IBD) treated with thiopurines, and as no data are available from Eastern Europe, this study was undertaken to analyze the incidence of non-Hodgkin lymphoma in relation to drug exposure in a population-based Veszprem province database, which included incident patients diagnosed between January 1, 1977 and December 31, 2008.