Towards therapeutic disease control in inflammatory bowel diseases

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Chapter Seven

Risk of Malignant Lymphoma in Patients with Inflammatory Bowel Diseases, a Dutch Nationwide Study

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Abstract

Immune suppressant medications such as thiopurines and anti-tumor necrosis factor agents are important for maintaining disease control in most patients with inflammatory bowel diseases (IBD), however, their use have been associated with the development of malignant lymphoma. The purpose of this Dutch nationwide study was to estimate the relative risk of malignant lymphoma in IBD patients.

IBD patients who developed a lymphoma between 1997 and 2004 were identified using the Dutch National Database of PALGA. Data from confirmed cases were collected from individual hospitals, including data on Epstein Barr virus. The age-adjusted 8-years incidence of malignant lymphoma in the Netherlands was retrieved from the Central Bureau of Statistics.

Forty-two hospitals were visited and 285 matches evaluated in the total cohort of 17834 IBD patients. Forty-four lymphomas were observed resulting in a relative risk of 1.27 (95% CI: 0.92 – 1.68). Only 19 of 44 patients (43%) were exposed to AZA/6-MP. Remarkably, 92% of patients (11/12) with EBV positive lymphoma used AZA/6-MP, in contrast to only 19% patients (4/21) with EBV negative lymphoma, suggesting a strong relation between EBV positive lymphoma and thiopurine use.

This nationwide study does not suggest a significant overall increased risk for lymphoma in IBD patients. A distinct correlation between EBV positive lymphoma and AZA/6MP use was observed.

Introduction

An approximate fourfold increased risk of a malignant lymphoma in inflammatory bowel disease (IBD) patients treated with azathioprine/6-mercaptopurine (AZA/6MP) was observed in a meta-analysis several years ago. [1] Since the absolute risk was considered low and not affecting the risk-benefit ratio, global IBD guidelines continued to endorse the use of AZA/6MP as maintenance therapy for IBD. Two recent developments have occurred that could potentially challenge this. First, reports on cases with hepatosplenic T-cell lymphoma suggested a role for thiopurines possibly in combination with anti-TNF therapy. [2] Second, a recent French prospective nationwide study from the Cesame Study Group involving almost twenty thousand IBD patients, demonstrated a significant increased risk for lymphoma development in patients receiving thiopurine therapy. [3]

IBD lymphoma cases have typically involved post-transplant lymphoproliferative disorder-like B-cell disorders associated with Epstein-Barr virus suggesting a causal role for immunosuppression. However, inflammation itself might contribute to the excess lymphoma risk. Indeed, a longer duration of IBD was an independent risk factor for developing a lymphoma in the Cesame study. Also, in rheumatoid arthritis it has been evident that severe disease can be associated with an increased risk for lymphoproliferative disease irrespective of immunomodulatory therapy. [4, 5]

Although the cumulative absolute risk for developing lymphoproliferative disorders in patients receiving thiopurine therapy appears to be low, we investigated the lymphoma incidence in a Dutch nationwide study. Specifically, we were interested in the association between the use of thiopurines and the development of lymphoproliferative disorder-like B-cell disorders in IBD patients associated with EBV.

Methods

Cases

To identify all IBD patients in the Netherlands who developed a malignant lymphoma, the PALGA database was used. PALGA is the Dutch nationwide network and registry of histo- and cytopathology, which contains standardized abstracts of all 16 million inhabitants of the Netherlands since 1990. [6] Patients in this registry are identified by date of birth, gender and the first 4 characters of their family name. The abstracts contain encrypted patient information, demographic data and a summary of the pathology report coded in accord with Systematized Nomenclature of Medicine (SNOMED) terminology issued by the College of American Pathologists. We queried the PALGA database according to a standardized procedure, after which an independent review committee consented to this search and subsequent identification of cases. The PALGA case-numbers were generated in an anonymous way. Subsequently, local pathologists were contacted to identify the associated medical files. Local gastroenterologists or treating physicians assisted to retrieve the required datasets. Finally, participating hospitals were visited and anonymized datasets of case reports matched by PALGA were entered in the case report forms (CRFs) using unique study numbers.

Dutch lymphoma incidence and expected number

Age-adjusted incidence numbers of Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL) in the general population in the Netherlands were obtained from the Central Bureau for Statistics (2000 – 2004) and used to calculate the 8-years incidence and subsequently the expected number in our IBD-cohort. The total number of the cohort was calculated using the estimated sum of patients per participating hospital and was estimated at 23216. Because 23% of the case histories was not available for full analysis, the final cohort size was estimated at 17834 IBD patients (77% * 23216). Forty-two medical centers were participating in this study, both academic and peripheral, and we used the Dutch age and gender specific incidence numbers from the Central for Statistics to calculate the number of IBD patients in each age and gender group.
Subsequently, the expected number of lymphomas in IBD patients was calculated using the 8-years age-adjusted incidence numbers.

Design of the study

From the PALGA registry all patients with both IBD and lymphoma were selected between 1997 and 2004. This time window was chosen since thiopurine therapy management became more prominent and more generally applied around 1995. Criteria adopted for the data base search were based on the association of the term "ulcerative colitis", "Crohn's disease", "inflammatory bowel disease", "inflammation", with "malignancy" and "malignant lymphoma" coupled to "oesophagus", "stomach", "small intestine" or "colon". The search disclosed only cases recorded between 1st January 1997 and 31st December 2004. Lesions histologically diagnosed as "multiple myeloma", or "adenomatous polyposis coli" as well as "colorectal carcinoma" were excluded from the study. When it wasn't clear whether the diagnosis was UC or CD, the diagnosis of the latest pathology report and/or medical file was recorded as definite diagnosis. When the diagnosis was "nonspecific colitis", and the patient used immunosuppressive agents, it was assumed that the patient had either CD or UC, and was recorded in the CRF as "IBD" and was subsequently verified in the individual medical file. The final selection of the cases was done after an analysis of the medical records in the participating hospitals. Cases were excluded if the objective diagnosis of lymphoma or IBD was lacking.

Data management and statistical analysis

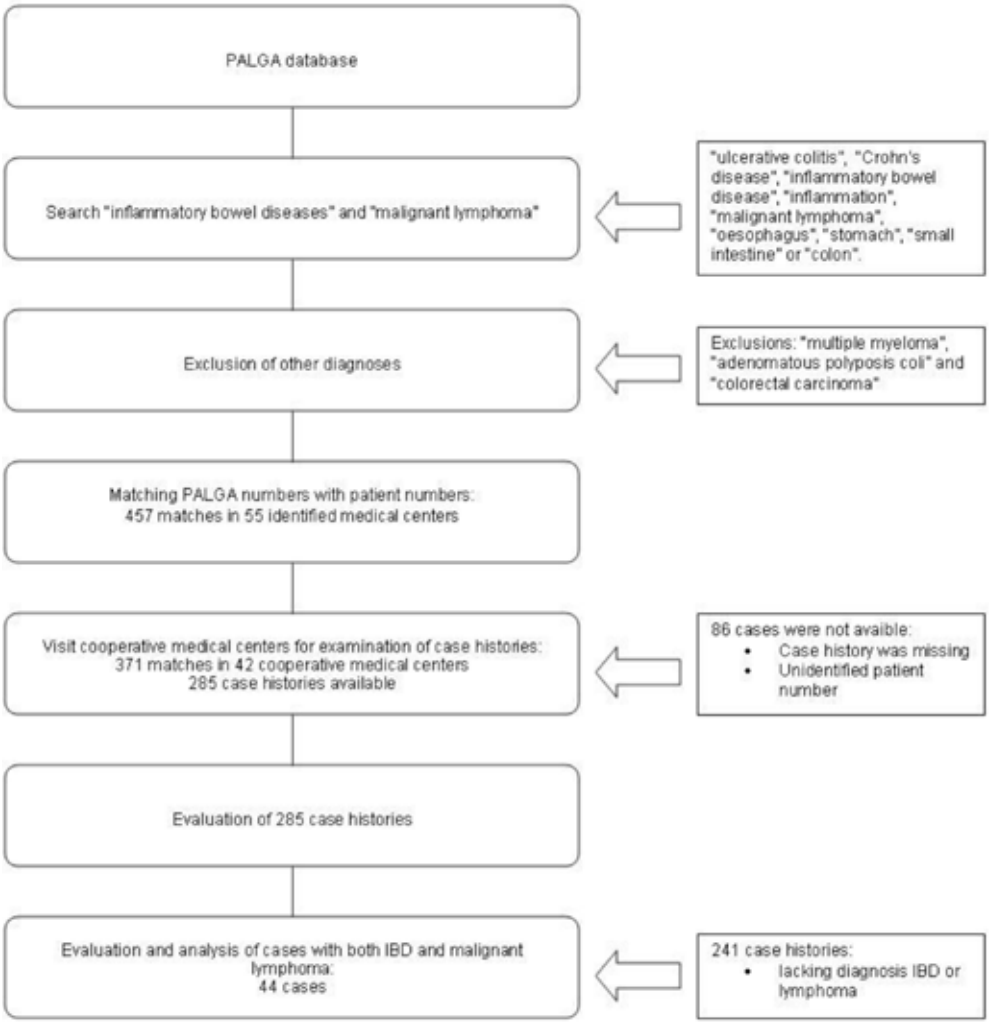
From all cases an *a priori* defined dataset was retrieved and entered in a dedicated Excel database. The dataset included both general information such as gender, age, height and weight, as well as details on disease duration, medication, onset of disease, and phenotypic characteristics such as stenoses, fistulas, surgery, complications and family history of IBD. In addition, the year of diagnosis of malignant lymphoma, location and type of lymphoma, treatment, patient survival and the presence of EBV were retrieved. Descriptive and analytical statistics were performed using Microsoft Excel. The relation between EBV positive lymphoma and azathioprine was calculated using Fisher exact test.

Results

Cases

The PALGA database search identified a total of 371 cases with both IBD and lymphoma between 1997 and 2004. Figure 1 depicts the search and selection algorithm. Eighty-six case histories (86/371, 23%) proofed not to be present for full analysis and could therefore not be analyzed. Subsequently, 42 Dutch medical centers were visited to analyze the medical files of in total 285 matches. In 241 cases, an objective diagnosis of IBD or malignant lymphoma could not be confirmed. Thus, 44 cases of malignant lymphoma in a cohort of 17834 IBD patients were included for final analysis. Table 1 shows the number of cases and patient characteristics.

Figure 1 Search and selection strategy.



Lymphoma risk

Since 44 cases were observed in a total IBD population of 17834, and 34.63 cases were expected (Table 2), the relative risk (RR) of developing a malignant lymphoma was 1.27 (95% CI 0.92 – 1.68). Hence, no overall increased risk was observed. However, a statistically significant increased risk was observed in the age categories 35 – 39 (RR 9.32, 95% CI: 3.89 – 17.07) and 45 – 49 (RR 3.99, 95% CI: 1.22 – 8.36). The increased RR in these two groups suggests an association between lymphoma and a diagnosis of IBD for patients of these ages.

Also, a gender specific analysis was performed, since the lymphoma incidence numbers in males are higher than in females and therefore, the expected number of lymphoma in males would be higher. In line with this, more lymphomas were observed in males (27/44, 61%) than in females (17/44, 39%). In all age groups taken together, the risk in males and females was similar, and there was no significant increased risk for either males or females for lymphoma in IBD (males: RR: 1.21 95% CI 0.79 – 1.72; females: RR: 1.23 95% CI: 0,70 – 1,89). However, in both males and females, a statistically significant risk was found in the age group 35 – 39 y and this increased relative risk was particularly outspoken in males (males: RR: 10.25 95% CI: 2.56 – 23.05; females: RR: 6.74 95% CI: 1.20 – 16.77). In all other

Table 1 Characteristics of cases.

	EBV positive	*EBV negative*	*EBV status unknown*	*Total*
number of cases	12/44 (27%)	21/44 (48%)	11/44 (25%)	44
Age				
mean ± SD (y)	46.75 ± 17.56	53.62 ± 14.31	61.64 ± 13.74	53.75 ± 15.74
median (range, y)	37.5 (24 – 78)	58 (21 – 74)	63 (36 – 79)	56.5 (21 – 79)
Male (%)	5/12 (42%)	15/21 (71%)	7/11 (64%)	27/44 (61%)
IBD				
CD	6/12 (50%)	6/21 (29%)	3/11 (27%)	15/44 (34%)
UC	6/12 (50%)	12/21 (57%)	6/11 (55%)	24/44 (55%)
IBDU		3/21 (14%)	2/11 (18%)	5/44 (11%)
Duration between IBD and lymphoma				
mean ± SD (y)	12.05 ± 6.75*	13.76 ± 10.97	12.73 ± 8.21	13.06 ± 9.21
median (range, y)	13 (2.5 – 25)	12 (0.5 – 36)	11 (1 – 31)	12 (0.5 – 36)
AZA/6MP use (%)	11/12 (92%)**	4/21 (19%)**	4/11 (36%)	19/44 (43%)
Duration of AZA/6MP use mean ± SD (y)	4.32 ± 4.08	3.63 ± 1.7	1.3 ± 0.71***	3.58 ± 3.3
median (range, y)	3 (0.25 – 12)	3.25 (2 – 6)	1.33 (0.58 – 2)	2.5 (0.25 – 12)

EBV = Epstein Barr virus, CD = Crohn's disease, UC = ulcerative colitis, IBDU = unspecified IBD, AZA = azathioprine, 6MP = 6-mercaptopurine

* of 1 patient in this group the time between IBD diagnosis and lymphoma was unknown; ** medication use of 1 patient in both groups was unknown; *** of 1 patient in this group the duration of azathioprine use was unknown

age groups, the relative risk for both males and females was similar and not significantly increased. In conclusion, males initially have a higher risk of developing lymphoma, and the fact that we observed more male than female cases, is therefore probably not related to IBD or treatment.

EBV associated lymphomas

Of the 44 lymphoma specimens, 12 were EBV positive and 21 negative. In 11 cases the EBV status could not be ascertained. Table 3 depicts the 12 individual IBD cases with an EBV-related lymphoma in detail. Of these, 11 patients were treated with thiopurines in combination with 5-ASA and prednisone. One case is supposed to be related to immunosuppression after liver transplantation. Six patients were diagnosed with CD (4 female and 2 male), 6 with UC (3 female, 3 male). None of the patients used anti-TNF compounds. Nine out of twelve lymphomas were localized in the gastrointestinal tract and all EBV+ lymphomas but one were of the diffuse large B cell type. A considerable variation was found in the dose and duration of the thiopurine use (duration ranging from months to 12 years, dose ranging from 50 – 350 mg/day), and in time between onset of IBD and lymphoma diagnosis (2.5 – 25 years).

Table 2 Expected and observed numbers of lymphoma and IBD in the cohort (1997 – 2004).

Age	*Expected number of cases*	*Observed number of cases (EBV positive lymphoma)*	*RR (95% CI)*
0 – 4	0.002	0	
5 – 9	0.013	0	
10 – 14	0.044	0	
15 – 19	0.318	0	
20 – 24	0.748	2 (1)	2.67 (0.23 – 7.79)
25 – 29	0.975	0	
30 – 34	0.783	2 (1)	2.56 (0.22 – 7.45)
35 – 39	0.858	8 (5)	9.32 (3.89 – 17.07)*
40 – 44	1.188	1	0.84 (0 – 3.37)
45 – 49	1.252	5 (1)	3.99 (1.22 – 8.36)*
50 – 54	1.834	3	1.64 (0.29 – 4.07)
55 – 59	1.924	5 (1)	2.60 (0.79 – 5.44)
60 – 64	2.136	6 (1)	2.81 (0.98 – 5.57)
65 – 69	3.370	4	1.19 (0.30 – 2.67)
70 – 74	4.913	4	0.81 (0.20 – 1.83)
75 – 79	5.729	4 (2)	0.70 (0.17 – 1.57)
80 – 84	5.022	0	
85 – 89	2.833	0	
> 90	0.788	0	
Total	34.63	44	1.27 (0.92 – 1.68)

Table 3 Characteristics of EBV positive lymphomas.

	Year of lymphoma diagnosis	*Age at lymphoma diagnosis*	*Sex*	*Aza / 6MP*	*Dose and duration*	*Lymphoma site*	*Lymphoma type*	*IBD*	*Time between IBD and lymphoma*	*Outcome*
1	2004	37	M	Y	Aza 200 mg/day 8 years	ileum	Diffuse large B	CD	15 years	RTX + surgery, survival
2	2001	35	M	Y	Aza 150 mg/day Months	sigmoid	Diffuse large B	UC	6 years	RTX + surgery, survival
3	2004	37	M	Y	Aza, 100 mg/day 8 years	lymph nodes, bone marrow, lungs, spleen, liver, stomach	Diffuse large B	CD	17 years	RTX, died 2004
4	2004	34	F	Y	Aza, 100-350 Mg/day 3 years	lungs, dermis, liver, kidney	Diffuse large B	UC	13 years	CHOP, survival
5	2001	36	F	Y	Aza, 100 mg/day 12 years	liver, perianal	Diffuse large B	CD	15 years	CAVmP, survival
6	2001	62	F	Y	Aza, 50 mg/day 3 months (1 y MTX for RA)	spleen, rectum	?	UC	2,5 years	CHOP, survival
7	2000	38	F	Y	Aza, 150 mg/day 2 y	dermis, lungs	?	CD	25 years	Remission and survival
8	2001	58	F	Y	Aza, 50-150 mg/day 4 years	perirectal	Diffuse large	CD	6 years	RTX, died 2001
9	2000	24	F	Y	6-MP 50 mg/day 1 year	stomach	?	UC	13 years	RTX, died of sepsis 2000
10	1999 (post mortem)	78	F	Y	Aza, 50-150 Mg, 1,5 y	brain	Follicular B cell	CD	4 years	Unknown, no survival
11	1999	46	M	Y	Aza, 100mg/day 1 year	Descending colon	Diffuse large	UC	16 years	Surgery, no survival
*12**	2003	76	M	N		Unknown	unknown	UC	unknown	Chemotherapy, survival

M = male, F = female, aza = azathioprine, 6-MP = 6-mercaptopurine, CD = Crohn's disease, UC = ulcerative colitis, RTX = rituximab

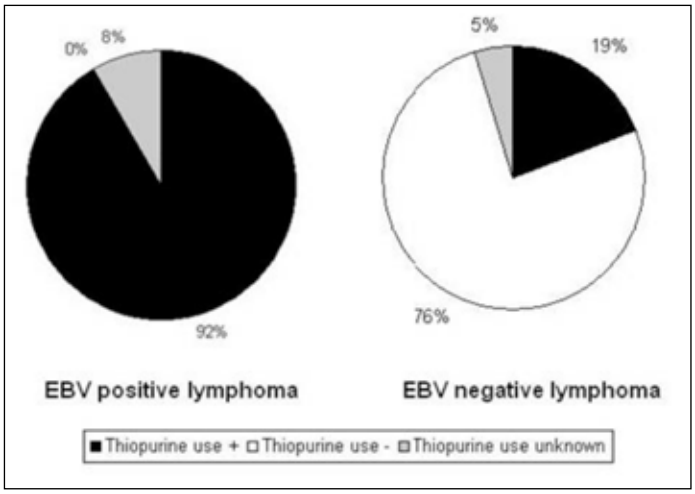
* In this case the EBV-positive lymphoma was thought to be related to immunosuppression after liver transplantation

Twenty-one EBV negative lymphomas were observed (Table 4). Of these, four patients used azathioprine. Nineteen patients used mesalazine, prednisone or a combination, one patient didn't receive any therapy at all and from one patient the prescribed medication was unknown. Of these 21 lymphomas, 10 lymphomas were diffuse large B cells lymphomas, so there was more variation in the type of lymphoma. Twelve out of 21 lymphomas were localized in the gastrointestinal tract. Twelve patients were diagnosed with UC (8 male, 4 female), six with CD (4 male, 2 female) and three with unspecified IBD (IBDU). The time between IBD and lymphoma diagnosis ranged from 6 months to 36 years.

Association between azathioprine/6-MP use and EBV positive lymphomas

Of the 44 cases, 19 patients were exposed to AZA/6MP (range: 3 months –12 yrs), 23 patients never used AZA/6MP and from two patients it was unknown whether they used AZA/6-MP. Of the 19 lymphomas in thiopurine users, 15 were tested for EBV. Remarkably, 11 lymphomas were EBV positive (73%) and 4 were EBV negative (27%), and there was a significant association between thiopurine use and EBV positive lymphoma ($p<0{,}001$). Twenty-three patients didn't use AZA/6MP, and in this group 16 lymphomas were tested for EBV status. No EBV positive lymphomas were found. From 2 patients it was unknown whether they used AZA/6-MP, one tested negative for EBV and one was positive for EBV. The latter case, however, was thought to be related to immunosuppression following liver transplantation (Figure 2 and table 5). Most EBV positive lymphomas were diffuse large B cell lymphomas. Ten out of 21 EBV negative lymphomas were diffuse large B cell lymphomas. Whether these lymphomas arose as a result of the disease itself or because of the use of immune suppressive agents has not been elucidated yet. Since EBV positive lymphomas arise especially in the setting of immunosuppression, the occurrence of these lymphomas suggested a strong relation with the use of immunosuppressive drugs, especially thiopurines, in IBD patients.

Figure 2 Thiopurine use in EBV positive and EBV negative lymphomas.



A significant association between EBV+ lymphoma and thiopurine use was found ($p \leq 0.001$)

Table 4 Characteristics of EBV negative lymphomas.

Pt no	*Year of lymphoma diagnosis*	*Age at lymphoma diagnosis*	*Sex*	*Aza / 6MP*	*Dose and duration*	*Other medication*	*Lymphoma site*	*Lymphoma type*	*IBD*	*Time between IBD and lymphoma*	*Therapy & Outcome*
1	2000	21	M	Y	3,5 y 100 – 200mg	pred	bone marrow, spleen, liver	T cell	CD	4 years	Chemo, no survival
2	2004	58	M	N	-	-	stomach	Diffuse large B cell, stage IV B	UC	29 years	Chop, survival
3	2000	53	M	N	-	5-ASA pred	liver	Diffuse large B cell	UC	29 years	Rituximab, Chop, no survival
4	2001	63	M	N	-	5-ASA	colon	Marginal zone B cell	UC	28 years	No therapy, survival
5	2004	40	F	Y	3 y, 50mg	5-ASA pred	dermis	T cell	UC	12 years	MTX, complete remission
6	2000	31	M	N	-	5-ASA pred	retroperitoneal	Diffuse large B cell	IBDU	6 months	Surgery, no survival
7	1999	47	F	N	-	5-ASA pred	retroperitoneal	Diffuse large B cell st IV	UC	22 years	CHOP, Survival (complete remission)
8	2001	59	M	N	-	5-ASA	mandibula, bone marrow	Diffuse large B cell	IBDU	5 years	Radiotherapy, chemo, no survival
9	2002	66	M	N	-	5-ASA	stomach	Follicular B cell	IBDU	19 years	Surgery and CHOP, no survival
10	2003	66	F	N	-	5-ASA	submandibular	Diffuse large B cell	CD	10 years	CHOP, no survival
11	2004	38	M	N	-	5-ASA	duodenum	B cell	UC	2,5 years	Autologous stem cell transplantation, survival

12	2002	48	M	N	-	5-ASA pred	retroperitoneal	follicular	CD	16 years	Radiotherapy, survival
13	1997	72	F	N	-	5-ASA	spleen	B cell	UC	6 months	Surgery, survival
14	2002	55	M	N	-	5-ASA	bone marrow, lymph nodes, spleen, liver, kidney	Follicular B cell	CD	5 years	CVP, no survival
15	2002	74	M	N	-	5-ASA pred	Submandibular	Follicular B cell	UC	17 years	CVP / CHOP survival
16	2000	69	M	N	-	5-ASA pred	supraclavicular	Mantel cell	UC	36 years	CHOP, no survival
17	1999	35	F	Y	2 y, 75 – 125mg	5-ASA pred	liver, spleen, bone marrow	Diffuse large B cell, st IV	UC	4 years	CVP / CHOP, no survival
18	2001	64	M	Y	6 y 50 – 50 mg	5-ASA pred	Rectum	Diffuse large B cell	UC	17 years	CHOP, survival
19	1998	59	M	?		?	Ileum	Diffuse large B cell	CD	Months?	No survival
20	1997	47	M	N		5-ASA	Liver	Diffuse large B cell	UC	23 years	CHOP, survival
21	1997	61	F	N		Pred 5-ASA	Coecum		CD	9 years	survival

Thio = thiopurine, pred = prednisone, EBV Pos = EBV positive

Table 5 Thiopurine use and EBV status.

EBV status	*Thiopurine use +*	*Thiopurine use -*	*Thiopurine use unknown*	*Total*
Positive	11**	0	1*	12
Negative	4	16	1	21
Unknown	4	7	0	11
Total	19	23	2	44

* In this case the lymphoma could also be related to immunosuppression after liver transplantation
** A significant association between EBV+ lymphoma and thiopurine use was found ($p \leq 0.001$)

Discussion

This nationwide study in the Netherlands suggests that there is no overall statistically significant increased risk of malignant lymphoma in IBD patients (RR 1.27, 95% CI: 0.92 – 1.68). Two relevant additional observations were made: 1) almost all patients with an EBV positive lymphoma used AZA/6-MP, and 2) these EBV post-transplant like lymphomas were particularly prevalent in the younger aged adult patients (< 50 years). This was a remarkable finding since the expected number of lymphomas increases with age and is quite low in younger age categories of the normal population. Therefore, these data suggest that younger aged adult patients may have an increased risk. Although more lymphomas were observed in males (61%), more lymphomas were expected since the lymphoma incidence in males is higher than in females. Both in males and females no significant increased risk for lymphoma was found, except in the age group 35 – 39. Risks were similar and not significantly increased for males and females in other age groups. Lymphomas of different origin were found in the study population, which included both CD and UC patients in different age categories. Since the study population is a mixed population and not all patients received immunomodulators, it is possible that the calculated risk underestimates the actual risk in patients receiving immunomodulators, and overestimates the risk in patients that do not.
The current literature does not offer clear and conclusive answers on the risk of predisposing factors for lymphoma development in IBD. It seems that our results are comparable to those of reported population based studies. Two large population based studies including 16996 IBD patients in the UK [7] and 47679 IBD patients in Sweden [8] failed to show a significant increased risk of lymphoma (RR for CD 1.4 and 1.3, RR for UC 1.2 and 1.0 resp.). In addition, other population based studies did not show a significant increased risk. [9-11]
In contrast, one population-based, retrospective Canadian IBD study did observe an increased risk of 2.4 in CD patients but not in UC. [12] In 2000, Farrell *et al.* observed a small increased risk in a cohort of 782 IBD patients. [13] In 2002, Dayharsh *et al.* observed in 10,000 IBD patients from a tertiary center a two-fold risk, also including EBV positive lymphomas. [14] Also, two other studies found a significant increased risk. [1, 3] Reasons for the conflicting results of the different studies could be the design of the study, selection of patients, referral bias, or a different incidence of NHL and HL in the general population. For instance, it is possible that single center studies experience referral bias, and meta-analyses performed on the cases reported in single center studies might overestimate the actual risk. In addition,

the prospective study performed by Beaugerie *et al*. showed a significant increased risk but was also designed differently; the investigators aimed to evaluate the lymphoma risk in thiopurine users versus non users. Because of differences in design and patient recruitment, it is complicated to compare the outcomes of different studies.

Furthermore, we found that especially younger aged adult patients are at risk. This observation is in line with another study [15] and rather interesting, since lymphoma incidence in the general population increases with age, and therefore the increased risk in the younger aged adult patients suggests that the lymphoma is more likely related to the disease or the treatment. However, it is not known why this age group might have an increased risk. Future studies are needed to elucidate why this particular group has an increased risk, and how this vulnerable group can be protected from an increased risk. Also, we confirmed a significant association between EBV positive lymphoma and the use of thiopurines. This was observed previously in other studies and case reports. [1, 16-18]

There has been a longstanding concern regarding anti-TNF therapy and the risk of lymphoma. Anti-TNFs were introduced in the Netherlands in the late '90s so anti-TNF was introduced during our study period (1997 – 2004). None of our cases used anti-TNF therapy, and the issue of anti-TNF therapy and the risk of lymphoma was not addressed in this study.

It is unclear to what extent disease severity plays a role in the development of malignant lymphoma in IBD. In rheumatoid arthritis (RA), a strong relation between disease activity and lymphoma risk has been reported. [4, 19] One particular problem with such an assumption is the selection bias of patients because association evidently does not imply causation. It is likely that use of thiopurine derivatives also reflects severity of the disease, which in itself could well be part of the pathogenesis of lymphoma development. This concern has also been voiced by others. [20]

A few limitations of this study should be noted. First of all, most medical centers in the Netherlands do not register their IBD patients in research dedicated databases. Consequently, the size of the total IBD patient cohort in our study is an estimation drawn from hospital information systems. Second, a considerable number of case histories could not be retrieved or were incomplete. As a result, we were unable to fully evaluate 23% of the possible cases. Although this a large percentage, the missing case reports were both in tertiary centers as well as peripheral centers and distributed over 21 medical centers, arguing against the idea of selection bias or over- or under presentation of a certain patient group and suggesting that the missing case reports over 21 medical centers are caused by random inaccuracies. In addition, given the number of medical centers included in our study (42 in total), the representativeness of our cohort and nationwide design of the study, this study provides a valid estimation of the relative risk of malignant lymphoma among IBD patients. We were unable to identify specific risk factors other than age in this study, since the design of this study is not eligible for the identification of other risk factors. Future studies are needed to identify other risk factors, such as disease severity, and to find out which patient groups are at risk.

In conclusion, we report no statistically significant overall increased relative risk for malignant lymphoma development in IBD patients, and a significant association of thiopurine derivative use and development of EBV-positive lymphoma. Furthermore, a significantly increased risk was found in younger aged adult patients. Should we now be reluctant to

prescribe thiopurines in our IBD population? Probably not, since thiopurine use has been so successful in maintenance therapy and in avoidance of corticosteroids, its benefit is well appreciated. In risk-benefit models, it has been suggested that a 10-fold risk is necessary for the overall effect of thiopurines in IBD to be detrimental. [21]

Competing interests: none to declare

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