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Fistulizing pattern in Crohn's disease and pancolitis in ulcerative colitis are independent risk factors for cancer: A single-center cohort study

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Risk factors

Abstract

Background & Aims: The combined role of immunomodulators (IMM) and clinical characteristics of Inflammatory Bowel Disease (IBD) in determining the cancer risk is undefined. The aim was to assess whether clinical characteristics of IBD are independent risk factors for cancer, when considering thiopurines and anti-TNFs use.
Methods: In a single-center cohort study, clinical characteristics of IBD patients with IBD duration $\geq$1 year and $\geq$2 visits from 2000 to 2009 were considered. Tests for crude rates and survival analysis methods were used to assess differences of incidence of cancer between groups. The methods were adjusted for the time interval between diagnosis and immunomodulatory treatments.
Results: IBD population included 1222 patients :615 Crohn's disease (CD), 607 ulcerative colitis (UC). Cancer was diagnosed in 51 patients (34 CD,17 UC), with an incidence rate of 4.3/1000 pt/year. The incidence rate of cancer was comparable between CD and UC (4.6/1000 pt/year vs 2.9/1000 pt/year ;p=n.s.). Cancer most frequently involved the breast, the GI tract, the skin. Lymphoma was diagnosed in CD (1HL,1NHL,0 HSTCL). Risk factors for cancer included

Abbreviations CD, Crohn's Disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IMM, immunomodulators; AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate; Anti-TNFs, anti-tumor necrosis factor alpha; EIM, extraintestinal manifestations; GI, gastrointestinal; OR, odds ratio; HR, hazard ratio; HSTCL, hepatosplenic T cell lymphoma.

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older age at diagnosis of IBD (CD: HR 1.25;95%CI 1.08–1.45; UC:HR 1.33;95%CI 1.15–1.55 for an increase by 5 years; p=0.0023; p=0.0002), fistulizing pattern in CD (HR 2.55; 95%CI 1.11–5.86, p=0.0275), pancolitis in UC (HR 2.79;95%CI 1.05–7.40 p=0.0396 *vs* distal). IMM and anti-TNFs did not increase the cancer risk in CD, neither IMM in UC (anti-TNFs risk in UC not feasible as no cases observed).

Conclusions: Fistulizing pattern in CD, pancolitis in UC and older age at diagnosis of IBD are independent risk factors for cancer.

1. Introduction

Thiopurines and anti-TNFs show a proven efficacy in Inflammatory Bowel Disease (IBD).[1] Thiopurines have been used since late 1960s in IBD.[2,3] An increased risk of lymphoma has been suggested in IBD patients treated with azathioprine (AZA) and 6-mercaptopurine (6-MP),[4–8] particularly in young patients with Crohn's Disease (CD).[9] Nevertheless, the absolute risk of lymphoma by using thiopurines in IBD appears to be small and the benefits have been reported to overwhelm the lymphoma risk.[1,9,10] This issue is however still debated, particularly due to the recent use of combined treatment with anti-TNFs.[1,11] As the first trial using Infliximab in IBD has been published in 1995,[12] the long-term outcome of patients treated with anti-TNFs is under investigation. Current evidences suggest that anti-TNFs with no thiopurines do not increase the cancer risk,[1,13–19] despite few discrepant findings.[20] Differently, evidences consistently indicate that combined treatment with thiopurines and anti-TNFs significantly increases the lymphoma risk in IBD.[1,21,22] Growing evidences describe the development of a rare hepatosplenic T cell lymphoma (HSTCL) after combined treatment with thiopurines and anti-TNFs, particularly in young male patients with CD.[1,21–26] This issue assumes relevance also in relation to the proven efficacy of this combined treatment, particularly in young patients with a severe IBD course.[1]

Despite several studies investigated the cancer risk associated with the use of immunomodulators (IMM) use in IBD, the role of clinical characteristics of IBD in determining this risk has been less extensively investigated. CD has been associated with lymphoma.[6–10,27] non-melanotic skin cancers[28] and breast cancer[29] even in patients with no history of IMM. Long-standing colitis and sclerosing cholangitis have been reported to increase the risk of colon cancer in IBD.[30] Most of these observations derive from monocentric studies, thus accounting for the observed discrepant findings.[31]

By our knowledge, few studies investigated the cancer risk when using IMM and/or biologics in patients with different clinical characteristics of IBD. This issue may currently assume relevance due to the worldwide use of IMM in young IBD patients, highly responsive to ISS and anti-TNFs.

On the basis of these observations, we aimed to assess, in a single-center cohort study, the role of clinical characteristics of IBD in determining the cancer risk in a cohort of IBD patients under regular follow up. In particular, we aimed to assess whether characteristics of IBD and/or of the host represent independent risk factors for cancer. The role of IMM drugs in determining the cancer risk has been also investigated in relation to clinical characteristics of IBD.

2. Materials and Methods

2.1. Study Population

In a single-center cohort study, clinical records of all IBD patients under regular follow up at our tertiary IBD referral Unit from 2000 to 2009 were reviewed. Clinical characteristics of IBD patients were prospectively recorded and defined according to current guidelines.[1,22,32] Inclusion criteria: a) diagnosis of IBD[1]; b) IBD duration $\geq$1 year including at least 2 visits at our referral center; c) no history of cancer before the diagnosis of IBD; d) no thiopurines and/or anti-TNFs use before the diagnosis of IBD; e) detailed clinical characteristics considered in the analysis. The following variables were reported in a database and considered: age at diagnosis of IBD, type of IBD (CD *vs* UC), IBD site/duration, CD behaviour (inflammatory, fistulizing, fibrostricturing), smoking habits, IBD surgery (yes/no), family history of IBD, extraintestinal manifestations (EIM), perianal disease, IMM use (AZA, 6-MP; methotrexate, MTX), including the date of administration (year), treatment duration and combination with anti-TNFs (Infliximab, Adalimumab, Certolizumab). For anti-TNFs, the dose and number of administrations[1] were reported. In order to analyze the effect of IMM on the incidence of cancer, IMM use was considered for patients treated with AZA, 6-MP and/or MTX for $\geq$3 months and anti-TNFs use for patients with $\geq$1 treatment. In patients with cancer, parameters considered included: date and patients' age (year) at time of diagnosis of cancer and site/histotype of cancer. In order to assess the role of IBD characteristics and to optimize control of potential confounding variables, the analysis of the incidence of cancer was carried out separately in UC and CD. As our study population includes patients with a diagnosis of IBD made both before and after the year 2000, it is a mixed cohort (prevalent and incident cohort respectively). Limits and observations supporting the absence of a substantial selection bias are detailed in the statistical analysis.

2.2. Statistical analysis

Differences in terms of characteristics between groups were assessed by the Wilcoxon-test (continuous variables) and by the Chi-square test (categorical variables). Associations between clinical characteristics and treatments were further investigated in a multivariate logistic regression. Crude overall incidence of cancer in subgroups was estimated in terms of rate per 1000 pt-years to adjust for different