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Thiopurines and Risk of Cancer in Patients with Inflammatory Bowel Disease - A Danish Nationwide Cohort study 1996-2018

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Background: Thiopurines are frequently used in patients with inflammatory bowel disease (IBD). The aim of this study was to assess the cancer risk of thiopurine monotherapy and thiopurine in combination with biologics compared to unexposed IBD patients.

Methods: Incident Danish IBD patients from 1996 to 2018 were identified in the national registers. Time at risk started at the date of IBD diagnosis and exposure status was time-dependent. Exposure was defined as registration of thiopurine and/or biologics. A lag period of 6 months was introduced at the first thiopurine registration as it was unlikely to have caused an effect on any immediate cancer case. If no new registration of thiopurines occurred 6 months from the last registration, the patient was assigned to the discontinued group. Non-melanoma skin cancer was analysed separately to avoid masking severe cancer forms and excluded from the overall cancer analyses. Cox regressions were performed to assess the risk of first cancer and risk estimates were presented as hazard ratios (HR) with 95% confidence intervals (CI). Only the incidence bar plot included non-IBD controls, matched on age, sex and municipality. Controls were unexposed to thiopurines.

Results: In total, 43,404 IBD patients were followed for a median of 8.2 years (IQR:3.7-14.2) from diagnosis. During follow-up, 7,736 Crohn’s disease (CD) (50.6%) and 6,632 ulcerative colitis (UC) patients (23.6%) were exposed to thiopurines. Cancer occurred in 1,292 (8.4%) CD and 1,840 (6.5%) UC patients. Both monotherapy and combination therapy were associated with developing any cancer (HR: 1.61 (95%CI:1.42-1.84) and (HR: 3.15 (95%CI:2.10-4.73), respectively) compared to unexposed IBD patients. In the elderly (>65 years), this was particularly apparent (Figure 1). The association between cancer and thiopurines was observed in non-melanoma skin-, melanoma-, urinary tract-, female genital organ-, lymphoid tissue-, colorectal- and digestive organ cancers. In patients who discontinued thiopurines, the HR returned to the level of unexposed HR: 1.01 (95%CI:0.91-1.13). The association with different cancer forms were higher in patients with >4 years and 1-4 years of thiopurine exposure, HR 1.58 (95%CI:1.37-1.82) and HR 1.24 (95%CI:1.07-1.44), compared to unexposed.

Conclusion: Thiopurines were associated with an increased risk of cancer in both mono- and combination therapy, especially in the elderly. This was noticeable in patients with 1-4 and >4 years of exposure, with 24% and 58% increased risk compared to unexposed. Reassuringly, discontinuation of thiopurines returned the risk to baseline and the absolute number of cancers was low. This warrants closer monitoring of all IBD patients, especially the elderly in combination therapy.

Figure(s)/Table(s): see next page
Inflammatory bowel disease: IBD.
Non-melanoma skin cancers were excluded.
Non-IBD controls were matched on age, sex and municipality. They were unexposed to thiopurines.