Editorial

Do Thiopurines Really Decrease the Risk of Colorectal Cancer in Ulcerative Colitis? The Light is Coming from Concept-based Subgroup Analyses

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In this issue of the Journal, Giordillo et al. assess the determinants of the risk of colorectal neoplasia in patients with ulcerative colitis [UC] from the ENEIDA Spanish cross-sectional cohort. Patients were eligible if they had at least one colonoscopy since UC diagnosis. The study period was the interval between UC diagnosis and last colonoscopy. In the multivariate analysis, the authors identified as protective factors the inclusion of patients in a surveillance colonoscopy programme (odds ratio [OR] 0.33; 95% confidence interval [CI]: 0.16–0.67), and any use of thiouropurines for more than 4 months from UC diagnosis (OR 0.21; 95% CI: 0.06–0.74). The authors conclude that thiopurine therapy reduces the incidence of colorectal neoplasia. This is a challenging statement because a recent meta-analysis concluded that there was no protective effect of thiopurines against colorectal cancer in UC patients at risk of colorectal neoplasia. In most of the nationwide studies, patients who were not at risk of colitis-associated colorectal cancer [patients with Crohn’s disease but without colitis or UC patients with isolated proctitis] have been included. This has never been the case to date for thiopurines. In this context, the chemopreventive effect of thiopurines on colorectal cancer in UC could be mainly due to non-specific anti-inflammatory properties, leading to reduced incidence of inflammation-driven colorectal neoplasia, providing that the ‘mean inflammatory burden’ of colonic mucosa is lower in patients exposed to thiopurines than in patients not exposed to the drugs.

Starting with this working hypothesis, we first understand why no chemopreventive effect of thiopurines against sporadic colorectal cancer has been demonstrated in patients treated with thiopurines outside the field of IBD, such as transplanted individuals. We should also postulate that the chemopreventive effect of thiopurines in IBD is restricted to patients at risk of inflammation-related colorectal neoplasia. In most of the nationwide studies, patients who were not at risk of colitis-associated colorectal cancer [patients with Crohn’s disease but without colitis or UC patients with isolated proctitis] have been included. This has never been the case to date for thiopurines. In this context, the chemopreventive effect of thiopurines against colorectal cancer in UC reported in studies from Rochester and New York, whereas the most recent study from Chicago suggested a marked protective effect of immuno-modulators on the risk of colorectal neoplasia [adjusted OR 0.24; 95% CI:0.08–0.74].

Among studies from tertiary care centres, there was no protective effect of thiopurines against colorectal cancer in UC reported in studies from Rochester and New York, whereas the most recent study from Chicago suggested a marked protective effect of immunomodulators on the risk of colorectal neoplasia [adjusted OR 0.24; 95% CI:0.08–0.74].

Concept-based critical review of study designs and results may be of some help in making things clearer. It is established that the sequence of molecular events differs notably between sporadic and colitis-associated cancers, but most elementary events are common to both types of cancers. Some molecular anti-carcinogenic effects of 5-aminosalicylates have been suggested. This has never been the case to date for thiopurines. In this context, the chemopreventive effect of thiopurines on colorectal cancer in UC could be mainly due to non-specific anti-inflammatory properties, leading to reduced incidence of inflammation-driven colorectal neoplasia, providing...
high risk of colitis-associated colitis, like in the CESAME study. The main result tells us that patients ever exposed to thiopurines are at reduced risk of colorectal neoplasia, but the causal relationship advocated in the title of the article is somewhat daring since the analysis was not adjusted for propensity to use drugs and the hypothesis of unmeasured confounders cannot be fully ruled out in observational studies.

Postulating on one side that sustained macroscopic and microscopic inflammation is the main driver of the risk of colitis-associated neoplasia, and on the other side that thiopurines are chemopreventive purely via their anti-inflammatory effects, opens the door for numerous unanswered questions: Have the other anti-inflammatory drugs used in the maintenance treatment of UC [5-amino-salicylates, anti-tumor necrosis factor agents] also a definite chemopreventive action? What is the best mucosal healer\(^1^4\) in UC? Is the best mucosal healer in UC also the best chemopreventive agent? Should we combine the treatments? Should we initiate the treatments from the diagnosis for the purpose of chemoprevention, aiming to prevent the molecular field changes\(^1^1\) that arise in colonic mucosa before the detection of neoplasia?

Despite a historical trend towards decreased frequency of colorectal cancer in IBD, possibly attributable to decreased colonic inflammation, the long-term risk of colorectal cancer remains a central element in the long-term prognosis of IBD, particularly in patients with extensive and early-onset colitis.\(^1^5\) In this context, the question of the chemoprotective effect of long-term IBD treatments is also essential. Much concept-driven tailored clinical research and epidemiology remain to be done in this field, and the current [ENEIDA, CESAME] and imminent [I-CARE] specifically designed observational prospective cohorts progressively emerge as indispensable pieces of the research arsenal, in addition to clinical trials and studies from medico-administrative databases and tertiary care centre cohorts.

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