Chemoprevention for colorectal cancer in ulcerative colitis patients

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Colorectal cancer (CRC) is one of the most serious and feared complications of ulcerative colitis (UC), as it accounts for one-sixth of all deaths, in these patients. Particularly, patients with pancolitis and with a clinical history of more than 7-10 years are considered at highest risk for colon cancer; the cumulative incidence being 5-10%, 20 years after disease onset and 15-20% after 30 years. Concomitant primary sclerosing cholangitis (PSC), family history of CRC, backwash ileitis and early age at UC onset, may also contribute to the increase of the risk.

At present, the only effective method of cancer prophylaxis remains total proctocolectomy, but it is seldom an attractive option. On the other hand, endoscopy and biopsy-based surveillance, which has been used to detect dysplasia and CRC, at an early stage, has been haunted by low sensitivity, and pitfalls that concern the scattered distribution and the histological interpretation of dysplasia, the poor compliance of UC patients and, certainly, its uncertain cost effective impact on mortality from CRC. Yet, it remains the standard of practice, until better diagnostic tests are available.

As an alternative to early detection, primary chemoprevention appears to be a promising approach to prevention of cancer in UC patients.

Given that the increased risk of CRC associated with UC may be related to inflammation-associated damage to DNA, anti-inflammatory therapy emerges as an effective candidate for the prevention of colorectal carcinogenesis in UC. In this setting, modest risk reductions, have been demonstrated for sulfasalazine and 5-ASA (mesalazine), used for both induction and maintenance of remission therapy, in epidemiological retrospective studies. There is also supportive experimental evidence that 5-ASA agents increase apoptosis, decrease proliferation and inhibit the formation of aberrant crypt foci, as well as reducing the spontaneous mutation rate at a (CA) 13 microsatellite, a mutation linked with chronic inflammation. However, more data are needed before 5-ASA can be recommended for CRC prevention in IBD and, thereafter, compliance would be an important issue.

Additionally, in the literature, folate is considered to have a protective role against neoplastic progression. Folate is an important coenzyme in purine and pyrimidine synthesis, as well as in aminoacid metabolism, methylation of biogenic amines and the initiation of protein synthesis. Epidemiologic studies indicate an inverse relationship between dietary folate intake and CRC. Moreover, oral supplementation of folic acid has been linked with regression of premalignant lesions of the cervix and lung, in humans. On the contrary, folate deficiency facilitates the development of cancer after exposure to chemical carcinogens in animal models, whereas in humans it results in chromosomal damage at folate-sensitive fragile sites. In patients with UC, folate deficiency is not uncommon, due to intestinal losses from active disease, reduced oral intake, and reduced intestinal absorption from competitive inhibition from sulfasalazine. In three retrospective studies, UC patients with colorectal premalignant lesions or cancer had lower red blood cell folate levels than patients without malignancy and folate supplementation was associated with a lower incidence of dysplasia. Furthermore, a recent prospective study indicates that folate supplementation is effective in reducing cell proliferation abnormalities in the rectal mucosa of patients with UC, giving a biological cause-effect association for folic acid and colonic dysplasia. Nevertheless, so far, data support but do not prove a definite preventive role of folate, in longstanding UC.
Recently, ursodeoxycholic acid (UDCA) has also been indicated as a candidate for chemoprevention, from studies in animal models and in UC patients with PSC, who are at a remarkably high risk of CRC. Pardi et al., in a placebo-controlled trial, presented the only prospective analysis of the effect of UDCA in the development of colonic neoplasia in such patients. Although this study was not double blind and the surveillance protocol was suboptimal, there was a significant reduction in the risk of colonic neoplasia, similar to that observed in a retrospective study that used a more rigorous protocol, in UC/PSC patients. Therefore, provided that this observation is verified by well-designed prospective studies, UDCA may prove the ideal chemopreventive agent, at least for this subgroup of patients, since it is a well tolerated drug that has also been associated with improvement of the biochemical indices of liver function. Whether its chemoprotective effect would extend to all colitic patients, and whether UDCA can prevent neoplastic progression in patients who already have dysplasia or adenomas remain to be clarified.

Other substances, such as calcium, vitamins and ω-3 fatty acids, known to normalize the cell proliferation pattern in the rectal mucosa of patients at high risk of CRC are currently being studied, with no definite evidence of chemopreventive potential, to date.

Consequently, at present, rigorous prospective studies are needed to elucidate the antineoplastic properties of 5-ASA, folic acid and UDCA, as well as to provide more detailed knowledge of the earlier events in UC-related carcinogenesis. This may help to produce pharmacological means of preventing CRC. Chemoprevention for colitis associated colorectal cancer may prove effective in the future.

REFERENCES