

Mini Review

Controversies in Chemoprevention of Colorectal Cancer with Ursodeoxycholic Acid

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Submitted: 03 December 2013

Accepted: 06 January 2014

Published: 08 January 2014

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Keywords

- Ursodeoxycholic acid
- Chemoprevention
- Colorectal cancer

Abstract

Colorectal cancer (CRC) is one of the most common cancers among men and women in western countries. Both *in vitro* and *in vivo* data strongly suggest that ursodeoxycholic acid (UDCA), a tertiary bile acid found naturally in low concentrations in humans may protect against CRC. Human studies also suggest that UDCA inhibits tumor development in high-risk subjects and inflammatory bowel disease (IBD). On the contrary, more recent studies have portrayed higher cancer incidence in patients treated with UDCA. However, higher doses of UDCA are alleged for increased cancer incidences in these studies. Dual role of UDCA in chemoprevention is an important field for future investigations.

ABBREVIATIONS

UDCA: Urso Deoxy Cholic Acid; CRC: Colorectal Cancer; IBD: Inflammatory Bowel Disease; FAP: Familial Adenomatous Polyposis; APC: Adenomatous Polyposis Coli; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; COX-2: Cyclooxygenase-2; ACF: Aberrant Crypt Foci.

INTRODUCTION

Colorectal cancer (CRC) is a prominent cause of cancer-related mortality in United States. Therapies are still limited for advanced tumors. Since the cure rate for patients with advanced colon cancer remains grim, efforts to identify effective chemopreventive strategies to prevent the development of this malignancy have received increasing attention [1]. Contenders for chemoprevention include individuals at high risk of diseases such as inflammatory bowel disease (IBD) and with inherited syndromes such as familial adenomatous polyposis (FAP), as well as patients with previous colorectal adenomas and carcinomas. Regular intakes of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and cyclooxygenase-2 (Cox-2) inhibitors significantly reduced the rates of CRC in various human trials [2]. However, gastrointestinal and cardiovascular toxicity could limit the widespread use of these inhibitors. Ursodeoxycholic acid (UDCA), 7- β -epimer of chenodeoxycholic acid (CDCA) has been extensively studied in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) patients. The

immunomodulatory, and cytoprotective effects of UDCA may account for the mechanisms of benefit in these patients [3]. More recently, UDCA has been investigated to reduce sporadic colon cancer risk in CRC patients.

DISCUSSION

In vitro cell culture studies

The molecular pathways by which UDCA affects colonic carcinogenesis are not completely understood. Several mechanisms in cell culture studies have suggested that UDCA, a more hydrophilic bile acid, may prevent neoplastic transformation by offsetting the tumor-promoting effects of secondary bile acid deoxycholic acid (DCA) [4-10]. Tumor promoting DCA induced apoptosis whereas UDCA inhibited cell proliferation [4]. UDCA induced caveolin-1 mediated degradation of epidermal growth factor receptor (EGFR) [5]. UDCA suppressed DCA-induced Cox-2 expression that requires transcription factor CCAAT/enhancer binding protein- β (C/EBP β) and stress mitogen-activated protein kinase-p38 (MAPK-p38) in colon cancer cells [6]. UDCA inhibited extracellular signal-regulated kinase (ERK) activation by DCA in human colon cancer cells [9] and also blocked nuclear factor- κ B (NF- κ B) activation, an important mechanism for anti-inflammatory effects of this cytoprotective bile acid [10].

In vivo animal studies

FAP is characterized by the mutations of the tumor suppressor

adenomatous polyposis coli (APC) gene and the development of thousands of adenomatous polyps in the colon. UDCA/sulindac combination treatment prevented intestinal adenomas in a mouse model of polyposis [11]. The carcinogen azoxymethane (AOM)-induced rodent model of experimental CRC recapitulates many clinical, histological and molecular features of human colon cancer. Dietary supplementation of UDCA significantly reduced the number of tumor-bearing rats and abolished the development of carcinoma in AOM model [12]. The tumor protective effect of UDCA was demonstrated both in initiation and tumor promotional phases [13]. UDCA also inhibited colitis-related mouse colon carcinogenesis in AOM/Dextran model [14]. These results initiated the idea of UDCA use in patients with sporadic colon cancer or ulcerative colitis (UC) to prevent dysplasia, adenomas and cancer. Subsequently, the protective effect of UDCA was demonstrated in aberrant crypt foci (ACF) stage, the earliest stage of premalignancy in rodent and human colon cancer. UDCA inhibited colonic hyperproliferation and ACF progression in the AOM model that involved suppression of cyclin D1 and Cox-2 and upregulation of E-cadherin expression [15,16]. A proto-oncogene, p21K-ras that regulates cyclin D1 and Cox-2 is frequently mutated in colon cancer. It was demonstrated that UDCA suppressed tumors with mutant or activated wild-type p21K-ras in AOM model and also repressed Cox-2 via both p21K-ras-dependent and -independent pathways [17]. UDCA also inhibited EGFR signaling both in normal mouse colon and in the AOM model [18]. EGFR signaling is required for microadenoma formation and tumor promotion by western high fat diet in the AOM model of colonic carcinogenesis [19]. Increased fecal DCA in western diet induces p21K-ras and Cox-2 via EGFR induction [20].

Clinical trials

Substantial pre-clinical data with UDCA strengthened the idea of UDCA use in diverse patient populations. Chemopreventive actions of UDCA have been investigated in patients that included subjects with colonic adenoma removal, IBD and FAP.

Adenoma Removal Group: There are two prospective and one retrospective study in this category. UDCA compared with placebo had no significant effect on colorectal mucosal proliferation in patients [21]. It was concluded that the duration of follow-up (6 months) was too short to detect any noteworthy effects of UDCA. In a randomized double-blind placebo-controlled trial, the preventative effect of UDCA (8–10 mg/kg/d vs placebo for 3 years) on adenoma recurrence was assessed in 1285 individuals who had undergone adenoma removal [22]. There was no significant difference in the overall rate of adenoma recurrence. However, a significant UDCA-related reduction in recurrence of adenomas with high-grade dysplasia was noted. Longer-term use of UDCA (>5 years) on the subpopulation of patients having highly dysplastic adenomas was suggested. Further, secondary analysis of this trial concluded that UDCA prevents advanced colorectal adenoma in men while increasing the odds in women with high fat intakes [23]. In PBC patients, a case-control study showed a similar beneficial effect with UDCA (13–15 mg/kg/d) on colorectal adenoma recurrence following removal [24].

Inflammatory bowel disease patients: Five studies have provided conflicting results of long-term UDCA treatment on

colonic dysplasia in patients with IBD with PSC [25–29] or without PSC [30]. In randomized 2-years of follow-up pilot study, 19 patients with IBD without PSC received UDCA treatment (500 mg b.i.d.) or a placebo. There was no significant difference in dysplasia progression or aneuploidy between the two groups [30]. UDCA use was negatively associated with the risk of colonic dysplasia in a retrospective analysis of 59 patients with UC associated with PSC [25]. On the contrary, in a cohort of 120 patients with UC and PSC, treatment with UDCA had no association with dysplasia or cancer occurrence [26]. However, the cumulative mortality was significantly lower suggesting a beneficial effect with UDCA. Two additional randomized controlled trials investigated the effect of UDCA on colorectal dysplasia at standard dosages (13–15 mg/kg/d) [27] and high dosages (28–30 mg/kg/d) [28] in patients with UC associated with PSC. The first retrospective study that analyzed a subgroup of 52/85 patients, beneficial effects with standard dosages of UDCA on colorectal dysplasia was demonstrated. In the second retrospective study, which analyzed a subgroup of 56/91 patients with a higher dose (28–30 mg/kg/d) of UDCA, the risk of dysplasia or CRC was significantly elevated in the UDCA group than in placebo group. However, if patients with possible adenoma lesions were excluded, high-dose UDCA was not associated with an increased risk of colorectal neoplasia. In another study, the increased risk of colorectal neoplasia with high doses of UDCA (17–23 mg/kg/d) was not established with a subgroup of 98/168 patients that presented no significant differences in dysplasia/cancer-free survival [29].

Familial adenomatous polyposis patients: Duodenal adenomas are the most common cause of death in FAP patients who have undergone prophylactic proctocolectomy. In a randomized, double-blinded, placebo-controlled study of 71 FAP patients, UDCA 10 mg/kg/d for 2 years had no effect on the development of duodenal adenomas [31]. In intention-to-treat analysis of 19 FAP patients for 6 months duration, celecoxib (400 mg twice daily)/placebo treatment significantly decreased polyp density. However, an increased polyp density was observed after a combination of celecoxib/UDCA (20–30 mg/kg/day) treatment, indicating high dose UDCA counteracts celecoxib in reduction of duodenal polyps [32]. Studies were extended to assess mRNA levels of potential risk parameters for malignant transformation. None of the evaluated parameters seems to be affected by either celecoxib alone or celecoxib and UDCA combination treatment. Surprisingly, Cox-2 levels in mucosa of FAP patients were very low conflicting previous reports [33].

CONCLUSION

Evidence from experimental animal models suggests that UDCA exerts chemopreventive activity against CRC. On the contrary, high dose UDCA demonstrated cancer promoting effects in clinical trials. UDCA appears to prevent adenoma recurrence, at least in male subjects. In patients with IBD, results were marred with different doses of UDCA and retrospective design, together with the high rate of patient exclusion. Randomized controlled prospective trials are urgently needed in this high-risk population. UDCA prevented adenomas in a mouse model of FAP. Nonetheless, UDCA at higher doses counteracted the protective effect of celecoxib in FAP patients. There is an urgent need to study molecular mechanisms to differentiate low and high dose UDCA actions in CRC prevention.

ACKNOWLEDGEMENTS

VA Merit Award (Project Id# 1171590; Project # 0001) and NCI Cancer Prevention R03 Grant (CA150081-02) to Sharad Khare.

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Cite this article

Khare T, Khare S (2014) Controversies in Chemoprevention of Colorectal Cancer with Ursodeoxycholic Acid. *JSM Gastroenterol Hepatol* 2(1): 1009.