HOW CAN WE PREVENT COLORECTAL CANCER WITH UDCA?

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Sevilla
Non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors can reduce the incidence and mortality of CRC. However, long-term use of NSAIDs is associated with substantial gastrointestinal toxicity and may cause an exacerbation in IBD patients. Selective COX-2 inhibitors are therefore attractive candidates for prevention.

- Low-dose aspirin for individuals carrying a high risk for CRC.
- Folate supplementation.
- Ursodeoxycholic acid decrease the incidence of colonic dysplasia in patients with ulcerative colitis and PSC and possibly reduces recurrence rates of polyps in general.
The great majority of CRC derives from adenomatous polyps. The sequence Adenoma-carcinoma has settled down for epidemic studies, histopathologicals and genetic. In 1989, Fearon and Vogelstein correlated this sequence with a series of genetic mutations.
CRC TUMORAL PROGRESSION

- **APC Mutation (5q) AND MCC (5q)**: Normal Epitelio
- **Hipomethylation DNA**: Early Adenoma
- **K-RAS Mutation (12p)**: Middle Adenoma
- **DCC LOST (18q)**: Late Adenoma
- **p53 DELETION (17p)**: Carcinoma

*Fearon y Vogelstein 1989*
### Characteristics % Carcinoma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>% Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIZE:</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 cm</td>
<td>1.3%</td>
</tr>
<tr>
<td>1 - 2 cm</td>
<td>9.5%</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>46%</td>
</tr>
<tr>
<td><strong>HISTOLOGY:</strong></td>
<td></td>
</tr>
<tr>
<td>Tubular (80-86%)</td>
<td>4.8%</td>
</tr>
<tr>
<td>Tubulovellous (8-16%)</td>
<td>22.5%</td>
</tr>
<tr>
<td>Vellous (3-16%)</td>
<td>40.7%</td>
</tr>
<tr>
<td><strong>DISPLASIA:</strong></td>
<td></td>
</tr>
<tr>
<td>Mild (70-86%)</td>
<td>5.7%</td>
</tr>
<tr>
<td>Moderate (18-20%)</td>
<td>18%</td>
</tr>
<tr>
<td>Severe (5-10%)</td>
<td>34.4%</td>
</tr>
</tbody>
</table>

(Muto T, Cancer 1975)
Secondary bile acids in stool, particularly deoxycholic acid (DCA), have been implicated in the pathogenesis of colorectal cancer:

- disruption of the balance between colorectal crypt cell proliferation, differentiation, and apoptosis.


Secondary bile acids appear to act by modifying intracellular signaling and gene expression.

Specifically, DCA appears to stimulate signaling through at least two different pathways that regulate the activity of activator protein-1.

DCA and other secondary bile acids are:

- Cytotoxic to colonic epithelial cells
- Mutagenically active in bacterial test systems.
- Associated with dysplasia
- Have antiapoptotic properties

However, the biological activity of ursodeoxycholic acid (UDCA), a tertiary bile acid, is diametrically opposed to that of DCA.

- UDCA suppresses many of the same pathways:
  - The mitogen-activated protein kinase pathway, that are activated by DCA.
  - Inhibit cell proliferation.
UDCA (3α,7β dihydroxy-5β-cholanic acid) is a tertiary bile acid which is more frequently used in the treatment of different cholestatic diseases.

It is normally present in human bile, but in a low concentration of only 3% of total bile acids.

The first reports on the effect of UDCA in patients with liver diseases appeared in Japan in 1961.

Several controlled trials using UDCA in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) have been published in the literature.

Chemopreventive mechanism

- Experimental evidence suggests three major mechanisms of action:
  1. Protection of cholangiocytes against cytotoxicity of hydrophobic bile acids.
  2. Stimulation of hepatobiliary secretion.
  3. Protection of hepatocytes against bile acid-induced apoptosis.

The CRC chemopreventive mechanism of UDCA is unclear:

- In animal models could lower the fecal contents and concentrations of secondary bile acid, which has co-carcinogenic potential in colorectal cancer.

- In patients with colorectal adenomas the levels of deoxycholic acid in serum correlated with the proliferation rates of the colorectal mucosa.
Ursodeoxycholic acid

UDCA AND ULCERATIVE COLITIS

UDCA AND ADENOMAS
Colorectal cancer in primary sclerosing cholangitis patients with ulcerative colitis is mostly right-sided where concentrations of carcinogenic secondary bile acids are highest.

**AIM:** To investigate whether ursodeoxycholic acid could be chemopreventive for colorectal cancer.

Patients with primary sclerosing cholangitis and ulcerative colitis

- 28 patients
- 92 controls

ursodeoxycholic acid

- The primary outcomes were colorectal cancer and dysplasia.
- The secondary outcome was overall mortality.
RESULTS:

The cumulative incidence of dysplasia or cancer was not significantly different between cases and controls (P = 0.17 by log-rank test).

The adjusted relative risk for cases of developing dysplasia or cancer was 0.59 (95% CI 0.26-1.36).

The cumulative mortality was significantly different between groups (P = 0.02 by log-rank test).

The adjusted relative risk for cases of death was 0.44 (95% CI 0.22-0.90).

**CONCLUSIONS:**

- In ulcerative colitis patients with primary sclerosing cholangitis, ursodeoxycholic acid did not reduce the risk of developing cancer or dysplasia.

- However, ursodeoxycholic acid may reduce mortality.


Nineteen patients (13 UC, 6 CD, median age 43 years) with long-standing, extensive IBD (median duration 21 years), with previous findings of low-grade dysplasia and/or DNA-aneuploidy.

Were randomized to receive either UDCA (500 mg b.i.d) (n=10) or placebo (n=9) in a controlled, double-blind, two-year study.

Colonoscopy with multiple biopsies for histopathology and for DNA-flow cytometry was performed at the start and at six-month intervals during the study period.

- The primary outcome was the need for colectomy due to progression of dysplasia.
- Changes in dysplasia and DNA-aneuploidy scores were also assessed.

RESULTS: There were no significant differences in the overall composed score between the two groups, either at study start or during the study period.

- In the placebo group one patient had a progression of dysplasia into high-grade and one patient developed a low-grade dysplasia; both had a colectomy.

- In contrast, no UDCA-treated patient had progression of dysplasia.

CONCLUSION:

- UDCA may prevent further progression of manifest low-grade dysplasia in colorectal IBD.
- Prolonged treatment or an increased dose may be needed to fully exploit the chemopreventive properties of this compound.

Results are contradictory but in general we observed that Ursodeoxycholic acid did not decrease the incidence of colonic dysplasia in patients with ulcerative colitis and PSC or UC alone.
Study results

Ramesh K et al. Ursodeoxycholic Acid Inhibits the Initiation and Postinitiation Phases of Azoxymethane-induced Colonic Tumor Development. Cancer Epidemiology, Biomarkers & Prevention 2002; 11: 1316-1321.
## Study results

<table>
<thead>
<tr>
<th>Diet group</th>
<th>Nº animals</th>
<th>Nº tumors</th>
<th>Tumor incidence</th>
<th>Tumor multiplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM alone</td>
<td>47</td>
<td>64</td>
<td>72,3</td>
<td>1.9</td>
</tr>
<tr>
<td>AOM + UDCA-1</td>
<td>39</td>
<td>26</td>
<td>46,2</td>
<td>1.4</td>
</tr>
<tr>
<td>AOM + UDCA-2</td>
<td>39</td>
<td>20</td>
<td>38,5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### Histology

<table>
<thead>
<tr>
<th>Diet Group</th>
<th>Adenomas</th>
<th>Carcinoma in situ</th>
<th>Invasive carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM alone</td>
<td>25 (39%)</td>
<td>28 (44%)</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>AOM + UDCA-1</td>
<td>15 (60%)</td>
<td>7 (28%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>AOM + UDCA-2</td>
<td>7 (35%)</td>
<td>11 (55%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

Ramesh K et al. Ursodeoxycholic Acid Inhibits the Initiation and Postinitiation Phases of Azoxymethane-induced Colonic Tumor Development. Cancer Epidemiology, Biomarkers & Prevention 2002; 11: 1316-1321.
**Conclusions:**

- They established that UDCA, when administered during tumor initiation or in the postinitiation (promotion/progression) phase, inhibits tumor development in the AOM model.

- Taken together with previous studies in humans, these results additionally support the potential efficacy of this bile acid as a chemopreventive agent in individuals at risk for colon cancer.

- Elucidation of the mechanisms by which UDCA inhibits colonic carcinogenesis may provide important insights into the signaling pathways involved in tumor promotion by secondary bile acids.

- Moreover, these studies may identify new targets for chemoprevention agents.

*Ramesh K et al. Ursodeoxycholic Acid Inhibits the Initiation and Postinitiation Phases of Azoxymethane-induced Colonic Tumor Development. Cancer Epidemiology, Biomarkers & Prevention 2002; 11: 1316-1321.*
A phase III, double-blind placebo-controlled trial of UDCA to evaluate its ability to prevent colorectal adenoma recurrence.

1285 patients undergone removal adenomas

661 patients
(UDCA 8-10 mg/Kg)

624 patients placebo

For 3 years or until follow-up colonoscopy.

Recurrence rates (nº of recurrent adenomas per unit time)
Proportions of participants with one or more recurrent adenomas.
### Study results

<table>
<thead>
<tr>
<th>Any adenoma</th>
<th>Placebo</th>
<th>UDCA</th>
<th>Placebo</th>
<th>UDCA</th>
<th>Placebo</th>
<th>UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with recurrence/total No. (%)</td>
<td>254/579 (43.9)</td>
<td>251/613 (41.0)</td>
<td>1.00 (referent)</td>
<td>0.89 (0.71 to 1.12)</td>
<td>1.00 (referent)</td>
<td>0.89 (0.70 to 1.12)</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
</tr>
<tr>
<td>No. with recurrence/total No. (%)</td>
<td>50/574 (8.7)</td>
<td>33/603 (5.5)</td>
<td>1.00 (referent)</td>
<td>0.61 (0.58 to 0.96)</td>
<td>1.00 (referent)</td>
<td>0.61 (0.39 to 0.96)</td>
</tr>
<tr>
<td>Any large adenoma§</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
</tr>
<tr>
<td>No. with recurrence/total No. (%)</td>
<td>60/579 (10.4)</td>
<td>54/613 (8.8)</td>
<td>1.00 (referent)</td>
<td>0.84 (0.57 to 1.23)</td>
<td>1.00 (referent)</td>
<td>0.84 (0.57 to 1.23)</td>
</tr>
<tr>
<td>Any villous histology</td>
<td></td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
</tr>
<tr>
<td>No. with recurrence/total No. (%)</td>
<td>42/574 (7.3)</td>
<td>46/607 (7.6)</td>
<td>1.00 (referent)</td>
<td>1.04 (0.67 to 1.60)</td>
<td>1.00 (referent)</td>
<td>1.05 (0.68 to 1.62)</td>
</tr>
<tr>
<td>Advanced lesion¶</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
</tr>
<tr>
<td>No. with recurrence/total No. (%)</td>
<td>110/579 (19.0)</td>
<td>99/613 (16.2)</td>
<td>1.00 (referent)</td>
<td>0.82 (0.61 to 1.11)</td>
<td>1.00 (referent)</td>
<td>0.83 (0.61 to 1.11)</td>
</tr>
<tr>
<td>Proximal location of adenoma#</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
</tr>
<tr>
<td>No. with recurrence/total No. (%)</td>
<td>121/578 (20.9)</td>
<td>110/610 (18.0)</td>
<td>1.00 (referent)</td>
<td>0.83 (0.62 to 1.11)</td>
<td>1.00 (referent)</td>
<td>0.83 (0.63 to 1.11)</td>
</tr>
</tbody>
</table>

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*David S. Alberts Phase III Trial of Ursodeoxycholic Acid To Prevent Colorectal Adenoma Recurrence. Journal of the National Cancer Institute, 2005; 97: 843-853.*
### Study results

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No recurrence</th>
<th>Nonadvanced adenoma only</th>
<th>Advanced adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, No. (%)</td>
<td>325 (56.1)</td>
<td>144 (24.9)</td>
<td>110 (19.0)</td>
</tr>
<tr>
<td>UDCA, No. (%)</td>
<td>362 (59.1)</td>
<td>152 (24.8)</td>
<td>99 (16.2)</td>
</tr>
</tbody>
</table>

*David S. Alberts Phase III Trial of Ursodeoxycholic Acid To Prevent Colorectal Adenoma Recurrence. Journal of the National Cancer Institute, 2005; 97: 843-853.*
Conclusions:

- UDCA treatment was associated with a non – statistically significant reduction in total colorectal adenoma recurrence.
- Nevertheless there is a statistically significant 39% reduction in recurrence of adenomas with high-grade dysplasia.
- Because severely dysplastic lesions have a high risk of progression to invasive colorectal carcinoma, this finding indicates that future chemoprevention trials of UDCA in individuals with such lesions should be considered.

*David S. Alberts Phase III Trial of Ursodeoxycholic Acid To Prevent Colorectal Adenoma Recurrence. Journal of the National Cancer Institute, 2005; 97: 843-853.*
To explain a chemoprotective effect against colon cancer, a reduced proliferation of the colorectal mucosal proliferation has been suggested.

The influence of UDCA on the proliferation of normal colorectal mucosa in humans.

Following endoscopic polypectomy, 20 patients with colorectal adenomas were randomized to receive either UDCA (750mg/day, n = 10, group A) or placebo (n = 10, group B) for 6 months in a double-blinded way.

Colorectal biopsies were sampled before and at the end of the medication by total colonoscopy.

Colorectal mucosal proliferation was measured by FACScan analysis of propidium iodine labeling.

Serum was sampled, and serum bile acids were analyzed by gas chromatography.

Study results

Conclusions:

In this study, UDCA treatment for 6 months does not seem to induce changes in the proliferative behavior of the colorectal mucosa in patients with adenomas.

It seems likely that a putative chemopreventive effect of UDCA in humans is not exerted by a reduction of the colorectal proliferation.

Sulindac was tested in combination with ursodeoxycholic acid for prevention of adenomas in the Min mouse model of adenomatous polyposis.

RESULTS: Ursodeoxycholic acid caused a dose-dependent decrease in the number of intestinal tumors.

Unlike sulindac and other nonsteroidal anti-inflammatory drugs, which are quite beneficial in the distal intestine but are somewhat less effective in the proximal small intestine (especially the clinically important periampullary duodenum).

Ursodeoxycholate had equal efficacy throughout the entire intestine, both proximal and distal.

Combined treatment with low-dose sulindac was less toxic, with normal weight gain and fewer gastrointestinal ulcerations than high-dose sulindac.

Combined treatment with sulindac and ursodeoxychololate was more effective than either agent alone for the prevention of tumors throughout the entire intestine.
CONCLUSIONS:

- These experiments provide the first evidence that ursodeoxycholic acid is effective for preventing adenomas in an animal model.

- Cyclooxygenase inhibition, when combined with this naturally occurring bile component, may become a promising approach for the prevention of colon cancer.
CONCLUSIONS

- UDCA could prevent recurrence of adenomas or even the development of CCR.
  - We need more controlled studies.

- Perhaps new dosage or drug combinations should be studied.