Perspective
Perspective on Carroll et al., p. 354

Cancer Prevention Research

Curcumin Chemoprevention: The Long Road to Clinical Translation

Imad Shureiqi[1,2], and John A. Baron[3]

Abstract

Curcumin exhibits significant antitumorigenic activity in various preclinical models; data supporting its chemopreventive activity in humans, however, are lacking. To our knowledge, the first published results of a phase II chemoprevention study of curcumin are reported in this issue of the journal by Carroll and colleagues (beginning on page ***354***), who examined the effects of oral curcumin on various putative biomarkers of colonic tumorigenesis in smokers. This perspective discusses the potential significance and limitations of the current study findings in addressing the question of whether curcumin is clinically active as a chemopreventive agent. *Cancer Prev Res; 4(3); 296–8. ©2011 AACR.*

The common food spice tumeric has been used as a medicine for millennia in India (1). Curcumin (diferuloylmethane), a polyphenolic natural extract of tumeric, modulates many putative molecular cancer targets, including cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-κB), tumor necrosis factor alpha (TNF-α), and cyclin D1, and exhibits significant anti-inflammatory and antitumorigenic activity in various preclinical models (2–6). Based on this promising preclinical activity, clinical studies have finally begun to test curcumin's chemopreventive effects in humans (7).

The safety and tolerability of oral curcumin quickly became evident in phase I studies, even when escalated to doses as high as 8 g per day (1, 7–9). However, the agent's low systemic bioavailability also became apparent in phase-1 pharmacokinetic studies (8–10). Healthy volunteers who received a single curcumin dose of less than 10 g had undetectable levels of curcumin in the serum in one phase I study (8). Nonetheless, longer oral intake of curcumin (3 months) achieved average serum levels of 0.51 μmol/L at a dose of 4,000 mg/day in a phase-1 study of 25 subjects with various premalignant lesions. The dose was escalated to 8,000 mg/day with little toxicity (9). A daily dose of 3.6 g of curcumin for 4 months also produced detectable serum and urine levels in another phase I study of colorectal cancer patients (11). This low bioavailability of curcumin has spurred research interest in developing a better formulation and chemical structure modification of curcumin to enhance its bioavailability (12, 13).

The low oral bioavailability of curcumin is due to its rapid metabolism, largely through conjugation to sulfates and glucuronides (14, 15). This metabolism may differ in some regards between humans and rodents (16), occurring in humans probably mostly in the gastrointestinal (GI) tract rather than in the liver (16). Whatever its underlying cause, the very low bioavailability of curcumin is puzzling in view of reports of possible systemic curcumin effects such as in treating inflammatory eye disorders (14). If these effects are real, it is not clear if they occur because of the potency of the amounts that reach the general circulation with high doses, because of the effects of unmeasured curcumin metabolites, or for other reasons.

Several clinical studies have been initiated to test the activity of curcumin against a range of cancers and other disorders (http://clinicaltrials.gov and ref. 14). Because oral curcumin seems preferentially distributed into colorectal mucosa (normal and malignant) compared with its distribution in other organs such as the liver (17), much clinical testing of curcumin has naturally focused on colorectal diseases, most notably colorectal cancer. Until now, the only clinical results available regarding the effects of curcumin in the colorectum come from a single report of 5 patients with familial adenomatous polyposis (FAP) treated with a combination of curcumin and quercetin (18). The numbers and sizes of polyps were reduced in all 5 patients after 6 months of treatment (18). Interpretation of this study, however, was limited by its small size, lack of control group, and the combination treatment arm.

The study reported by Carroll and colleagues in this issue of the journal (19) is thus a welcome addition to the curcumin literature. A small phase II study, it has the advantage of 2 treatment arms (but unfortunately no placebo). This open-label study enrolled smokers who had aberrant crypt foci (ACF) on screening colonoscopies.

Authors' Affiliations: Departments of [1]Clinical Cancer Prevention and [2]Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; and [3]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Corresponding Author: Imad Shureiqi, The University of Texas M. D. Anderson Cancer Center, Department of Clinical Cancer Prevention, Unit 1360, 1515 Holcombe Boulevard, Houston, TX 77030-4009. Phone: 713-745-4929; Fax: 713-794-4403. E-mail: ishureiqi@mdanderson.org

doi: 10.1158/1940-6207.CAPR-11-0060

Forty-one of the 44 patients completed the protocol prespecified 30-day treatment of daily curcumin at either 2 g (22 patients) or 4 g (19 patients). The primary study endpoint was the change in the levels of prostaglandin E_2 (PGE_2) and 5-eicosatetraenoic acid (5-HETE) levels in ACF and normal colonic mucosa samples obtained via endoscopy before and after curcumin treatment.

PGE_2 and 5-HETE are oxidative metabolites of arachidonic acid that have been linked to tumorigenesis (20–22). The selection of PGE_2 as a molecular biomarker has a particularly strong rationale: knockout of the PGE_2 receptor suppressed experimental carcinogenesis in the large bowel, and PGE_2 is clearly carcinogenic in colon models (23, 24). Cigarette smoke extract has been shown in preclinical models to promote colorectal tumorigenesis via increased production of PGE_2 and leukotriene B_4 (the terminal metabolite of 5-HETE; refs. 25, 26). Tobacco smoking has also been associated with an increase in the number of ACF (27) and with the production of PGE_2 and leukotriene B_4 in humans (28). Change in the number of rectal ACF and in the cell-proliferation marker Ki-67 expression was measured as secondary endpoints.

The choice of ACF as a biomarker of carcinogenesis has limitations. The majority of ACF detected endoscopically in humans are hyperplastic, not dysplastic (29, 30), and the authors could not assess the histology of the lesions they studied. Although various animal studies of colonic tumorigenesis have supported the concept that ACF are early precursors of colorectal adenomas and cancer, the putative role of ACF as an intermediate biomarker of human colonic tumorigenesis has recently been challenged by findings of large clinical studies (29–31).

Carroll and colleagues' measurements of tissue and plasma levels of both natural curcumin and its conjugates with a highly sensitive mass spectrophotometry method provide some interesting (and unexpected) findings. In addition to documenting both the low bioavailability of curcumin and the predominance of the conjugated forms in the general circulation, the study reported a high prevalence of detectable curcumin conjugates in plasma at baseline. This last finding is surprising, as the low bioavailability of curcumin implies that detectable levels should only be seen in individuals using curcumin supplements. Perhaps low intake, if long-term, can suffice. If confirmed, the finding that individuals in the general population have detectable conjugate levels raises the possibility that serum measurements can be used in epidemiological studies of the curcumin association with disease occurrence.

Results involving the examined chemoprevention biomarkers were negative in most regards, showing no significant effects for curcumin on the primary endpoint PGE_2 or 5-HETE in either normal or ACF rectal mucosa. The authors interpreted these finding as providing evidence for a lack of effects of these eicosanoids on early stages of colonic tumorigenesis. In support of this conclusion, PGE_2 and 5-HETE levels were in fact similar between the normal and ACF mucosa, with a trend even toward higher levels in normal mucosa than in ACF. To further question the utility of these eicosanoids as carcinogenesis biomarkers, they also cited findings from a prior study showing that celecoxib, a selective COX-2 inhibitor, failed to reduce mucosa PGE_2 levels while inhibiting polyp formation in FAP patients (32). Findings from this and the current study could be interpreted as suggesting that PGE_2 promotes colonic tumorigenesis at stages later than ACF and adenomas. Of note, a recently published study has showed no significant change in leukotriene B_4 levels during colonic tumorigenesis (33), calling into question whether 5-HETE really is a biomarker for colorectal tumorigenesis. The current study is limited in assessing the role of these pathways in colonic tumorigenesis by its relatively small sample size and single pathological endpoint. Therefore these interesting results need to be interrupted with caution; future studies are needed to further examine the role of these and other eicosanoids as biomarkers for early colorectal carcinogenesis.

Curcumin treatment also showed no effects on Ki-67 expression. Unfortunately, apoptosis markers were not included, although prior studies have demonstrated that apoptotic measurements predict curcumin chemopreventive activity in preclinical models (34). Evaluation of apoptotic markers in future translational studies in this setting would be welcome.

An interesting finding of the study is that curcumin significantly reduced ACF numbers at the 4-g but not the 2-g daily dose level. Although tantalizing, the significance of this finding is uncertain. The uncertainty regarding the role of ACF as an intermediate biomarker of colorectal cancer makes interpretation of the result difficult, and the possibility of an unintentional bias in the ACF assessment cannot be totally excluded because the study endoscopists were unblinded to treatment status.

Whether curcumin might have effects in the colorectum through systemic or topical exposure is an unanswered question in the current study. The investigators utilized a highly sensitive mass spectrophotometry method for measuring curcumin and its metabolites in both serum and rectal tissue samples. Following curcumin treatment, some, but not all, subjects had detectable levels of either curcumin or its metabolites in rectal tissues. More important, the detection of curcumin and its metabolites in rectal tissues did not correlate with the reduction in ACF formation. These findings lend no support to the concept that curcumin suppression of ACF formation depended on its topical effects through rectal tissue bioavailability. Curcumin metabolites, however, were detected in the serum of all of the examined subjects in the 4-g dose group, a finding that might argue for systemic effects. Examination of whether curcumin serum metabolite levels were different between the 2 dose levels and between the responders and nonresponders could help address this question. The small number of subjects in the subgroups, however, will limit the statistical power of these analyses.

What is the significance of the current findings of Carroll and colleagues? The ACF results provide hints of efficacy

and could be one of the first signs of the long-anticipated clinical activity of curcumin for chemoprevention. Unfortunately, this study provides only hints, and confirmation of curcumin's activity continues to be elusive. The intriguing finding that curcumin metabolites may be a suitable avenue for observational studies could help to lay the groundwork for a full (expensive and time-consuming) randomized controlled clinical trial. We therefore need to stay tuned for more data from the completed and ongoing clinical studies of curcumin, which it is hoped will be reported soon to further address the question of whether curcumin is an effective chemopreventive agent in humans.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Received December 23, 2010; revised January 26, 2011; accepted January 26, 2011; published online March 3, 2011.

References

1. Singh S. From exotic spice to modern drug? Cell 2007;130:765–8.
2. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Med 1991;57:1–7.
3. Aggarwal B, Kumar A, Bharti A. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 2003;23:363–98.
4. Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, Rao CV, et al. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. Cancer Res 1999;59:597–601.
5. Ramachandran C, You W. Differential sensitivity of human mammary epithelial and breast carcinoma cell lines to curcumin. Breast Cancer Res Treat 1999;54:269–78.
6. Prakobwong S, Khoontawad J, Yongvanit P, Pairojkul C, Hiraku Y, Sithithaworn P, et al. Curcumin decreases cholangiocarcinogenesis in hamsters by suppressing inflammation-mediated molecular events related to multistep carcinogenesis. Int J Cancer . 2010. [Epub ahead of print].
7. Aggarwal BB, Surh Y-J, Shishodia S, Hsu C-H, Cheng A-L. CLINICAL STUDIES WITH CURCUMIN. In:Back N, Cohen IR, Kritchevsky D, Lajtha A, Paoletti R, editors. The molecular targets and therapeutic uses of curcumin in health and disease. US: Springer;2007. p. 471–80.
8. Lao C, Ruffin M, Normolle D, Heath D, Murray S, Bailey J, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006;6:10.
9. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001;21:2895–900.
10. Hsu CH, Cheng AL. Clinical studies with curcumin. Adv Exp Med Biol 2007;595:471–80.
11. Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, et al. Phase I clinical trial of oral curcumin. Clin Cancer Res 2004;10:6847–54.
12. Huang Q, Yu H, Ru Q. Bioavailability and delivery of nutraceuticals using nanotechnology. J Food Sci 2010;75:R50–7.
13. Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, et al. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochem Pharmacol 2008;76:1590–611.
14. Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. Curcumin: from ancient medicine to current clinical trials. Cell Mol Life Sci 2008;65:1631–52.
15. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm 2007;4:807–18.
16. Ireson C, Jones D, Orr S, Coughtrie M, Boocock D, Williams M, et al. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol Biomarkers Prev 2002;11:105–11.
17. Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA, et al. Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. Br J Cancer 2004;90:1011–5.
18. Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol 2006;4:1035–8.
19. Carroll RE, Benya RV, Turgeon DK, et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res 2011;4:354–364.
20. Rao CV, Simi B, Reddy BS. Inhibition of dietary curcumin of azoxymethane induced ornithine decarboxylase, tyrosine, protein kinase, arachidonic acid metabolism and aberrantcrypt foci formation in the rat colon. Carcinogenesis 1993;14:2219–25.
21. Shureiqi I, Lippman SM. Lipoxygenase modulation to reverse carcinogenesis. Cancer Res 2001;61:6307–12.
22. Myung S-J, Rerko RM, Yan M, Platzer P, Guda K, Dotson A, et al. 15-Hydroxyprostaglandin dehydrogenase is an *in vivo* suppressor of colon tumorigenesis. Proc Natl Acad Sci U S A. 2006;103:12098–102.
23. Mutoh M, Watanabe K, Kitamura T, Shoji Y, Takahashi M, Kawamori T, et al. Involvement of prostaglandin E receptor subtype EP(4) in colon carcinogenesis. Cancer Res 2002;62:28–32.
24. Watanabe K, Kawamori T, Nakatsugi S, Ohta T, Ohuchida S, Yamamoto H, et al. Role of the prostaglandin E receptor subtype EP1 in colon carcinogenesis. Cancer Res 1999;59:5093–6.
25. Ye YN, Wu WK, Shin VY, Bruce IC, Wong BC, Cho CH. Dual inhibition of 5-LOX and COX-2 suppresses colon cancer formation promoted by cigarette smoke. Carcinogenesis 2005;26:827–34.
26. Ye YN, Liu ES, Shin VY, Wu WK, Cho CH. Contributory role of 5-lipoxygenase and its association with angiogenesis in the promotion of inflammation-associated colonic tumorigenesis by cigarette smoking. Toxicology 2004;203:179–88.
27. Moxon D, Raza M, Kenney R, Ewing R, Arozullah A, Mason JB, et al. Relationship of aging and tobacco use with the development of aberrant crypt foci in a predominantly African-American population. Clin Gastroenterol Hepatol 2005;3:271–8.
28. Duffield-Lillico AJ, Boyle JO, Zhou XK, Ghosh A, Butala GS, Subbaramaiah K, et al. Levels of prostaglandin E metabolite and leukotriene E(4) are increased in the urine of smokers: evidence that celecoxib shunts arachidonic acid into the 5-lipoxygenase pathway. Cancer Prev Res 2009;2:322–9.
29. Lance P, Hamilton SR. Sporadic aberrant crypt foci are not a surrogate endpoint for colorectal adenoma prevention. Cancer Prev Res 2008;1:4–8.
30. Gupta AK, Schoen RE. Aberrant crypt foci: are they intermediate endpoints of colon carcinogenesis in humans? Curr Opin Gastroenterol 2009;25:59–65.
31. Mutch MG, Mph RE, Fleshman JW, Rall CJ, Dry S, Seligson D, et al. A multi-center study of prevalence and risk factors for aberrant crypt foci. Clin Gastroenterol Hepatol 2009;7:568–74.
32. Sinicrope FA, Half E, Morris JS, Lynch PM, Morrow JD, Levin B, et al. Cell proliferation and apoptotic indices predict adenoma regression in a placebo-controlled trial of celecoxib in familial adenomatous polyposis patients. Cancer Epidemiol Biomarkers Prev 2004;13:920–7.
33. Shureiqi I, Chen D, Day RS, Zuo X, Hochman FL, Ross WA, et al. Profiling lipoxygenase metabolism in specific steps of colorectal tumorigenesis. Cancer Prev Res 2010;3:829–38.
34. Samaha HS, Kelloff GJ, Steele V, Rao CV, Reddy BS. Modulation of apoptosis by sulindac, curcumin, phenylethyl-3- methylcaffeate, and 6-phenylhexyl isothiocyanate: apoptotic index as a biomarker in colon cancer chemoprevention and promotion. Cancer Res 1997;57:1301–5.

Cancer Prevention Research

Curcumin Chemoprevention: The Long Road to Clinical Translation

Imad Shureiqi and John A. Baron

Cancer Prev Res 2011;4:296-298.