Published OnlineFirst April 14, 2008; DOI: 10.1158/1940-6207.CAPR-08-0049

Perspective

Clinical Prevention of Recurrence of Colorectal Adenomas by the Combination of Difluoromethylornithine and Sulindac: An Important Milestone

Michael B. Sporn[1] and Waun Ki Hong[2]

The spectacular clinical results reported by Meyskens, Gerner and colleagues in a lead article (1) of this very first issue of this new *AACR* journal on cancer prevention represent a landmark advance in efforts to stop the current worldwide epidemic of cancer deaths. This study also sets a new, exceptionally high standard for future clinical research on the chemoprevention of cancer.

This article is of great importance for many reasons. The authors show conclusively that the combination of low doses of two drugs, each relatively ineffective as preventive agents when given singly at low doses, caused a striking inhibition of colorectal adenomas in a large study involving almost 300 patients, all of whom had a previous resection for such adenomas and were thus at high risk for recurrence. The drugs used were difluoromethylornithine (DFMO), an inhibitor of polyamine synthesis, and sulindac, an anti-inflammatory drug, and they were given safely in combination over a 3-year study period with almost no adverse effects.

These new results represent the first demonstration of the clinical validity of the basic concept of "combination chemoprevention," first proposed in 1980 (2, 3). The magnitude of the combined chemopreventive effect of the two drugs is stunning. Overall, the incidence of adenoma recurrence was reduced 70%, from 41% in the control population to 12% in the patients treated with the drug combination. Even more striking are the effects on the number and severity of new adenomas. Thus, only 1 patient in the treated group was found to have multiple adenomas at the final colonoscopy, compared with 17 patients in the placebo control group, a 95% reduction compared with control. Furthermore, at the end of the study, 11 patients in the placebo group had advanced adenomas (at least 1 cm in size in 9 of these patients), whereas only a single patient in the treated group had an advanced adenoma, a >90% reduction compared with control. All of these preventive effects are highly statistically significant ($P < 0.001$). Such a marked level of preventive activity has never been seen before in any clinical chemoprevention trial involving any organ site. The practical clinical chemopreventive activity of the DFMO-sulindac combination reported here is clearly superior to that which has previously been shown for any of the nonsteroidal anti-inflammatory drugs, including aspirin, celecoxib, and rofecoxib, for suppression of adenomas (4–8).

The lack of any significant toxic side effects of the DFMO-sulindac combination in this study is extremely important. Meyskens, Gerner and colleagues have deliberately chosen to use the lowest possible effective doses of both drugs as an approach to avoid toxicity. Elegant previous "dose de-escalation" studies with DFMO have been particularly important in this regard. Thus, in two large clinical studies started more than 10 years ago, the present investigators determined the lowest dose of DFMO that would deplete levels of polyamines in the target tissue, colorectal mucosa (9, 10). The dose of sulindac used in the present study was only one half that used in a previous study that showed efficacy in treatment of colonic and rectal adenomatous polyps (11). This dose de-escalation approach is in marked contrast to conventional treatment studies in clinical oncology, in which doses of drug are escalated to determine the maximum tolerated dose before a full-scale treatment protocol is actually begun. Concerns about safety are a recurring theme in the objections of both oncologists and prospective patients to the general concept of chemoprevention. In response to these concerns, the present study has definitively shown that chemoprevention with combinations of low doses of drugs is an ideal way to diminish toxicity, while at the same time obtaining desired therapeutic synergy and efficacy.

There are several aspects of the pharmacology of both DFMO and sulindac that are worthy of comment. First of all, neither drug is new; both were synthesized for the first time more than 30 years ago, and they have been in clinical or experimental use for almost as long. Furthermore, neither drug fits currently fashionable paradigms for development of new cancer drugs. Neither DFMO nor sulindac is targeted to control a specific genetic mutation relevant to carcinogenesis. Both DFMO and sulindac are classic multifunctional drugs, the exact opposite of the targeted "magic bullets" that are so currently fashionable.

If one looks for any functional selectivity of DFMO beyond inhibition of polyamine synthesis (by virtue of its potent irreversible inhibition of ornithine decarboxylase), there is no compelling evidence to suggest that DFMO has a unique genetic target. DFMO inhibits polyamine synthesis, and increased polyamine synthesis has been known to be associated with cell growth and cancer for almost 50 years (12). The reported association of *myc*, *APC*, or *Kras* with the expression of ornithine decarboxylase (12) does little to explain the overall chemopreventive activity of DFMO; these are associations related to upstream control of ornithine decarboxylase expression, and do not address more significant and still unanswered questions of downstream targets of polyamines. There is no known unique signal transduction pathway regulated by DFMO, although many investigations have attempted to fit this drug into one. DFMO, although a specific

Authors' Affiliations: [1]Department of Pharmacology, Dartmouth Medical School, Hanover, New Hamsphire, and [2]Division of Cancer Medicine, M. D. Anderson Cancer Center, Houston, Texas
Received 03/03/2008; accepted 03/07/2008.
Requests for reprints: Michael B. Sporn, Department of Pharmacology, Dartmouth Medical School, 7650 Remsen, Hanover, NH 03755. Phone: 603-650-6557; Fax: 603-650-1129; E-mail: michael.sporn@dartmouth.edu.

doi:10.1158/1940-6207.CAPR-08-0049

Published OnlineFirst April 14, 2008; DOI: 10.1158/1940-6207.CAPR-08-0049

ornithine decarboxylase inhibitor, ultimately exerts its desired effects by altering entire cellular regulatory networks controlled by polyamines (13). DFMO is thus a classical multifunctional drug, and its overall action to suppress carcinogenesis cannot be explained in a simple reductionistic cartoon.

As for sulindac, it is not even a single drug because it is a prodrug that is metabolized into two principal active species, sulindac sulfide and sulindac sulfone, which have very different mechanisms of action (14, 15). Sulindac sulfide is a cyclooxygenase (COX) inhibitor, but like most older nonsteroidal anti-inflammatory drugs, it inhibits both COX-1 and COX-2, thereby lessening the life-threatening cardiovascular risks associated with selective COX-2 inhibitors such as celecoxib or rofecoxib (16, 17). In this cardiovascular context, the lack of selectivity of sulindac is a benefit, not a disadvantage, when sulindac is compared with celecoxib or rofecoxib. Furthermore, at the low dose of sulindac used in the present study, adverse gastrointestinal events were not significantly increased, as might have occurred with a higher dose of a nonselective COX inhibitor.

The other important metabolite of sulindac is sulindac sulfone (exisulind), which itself is the object of much current investigation. In contrast to the sulfide metabolite of sulindac, the sulfone is not a COX inhibitor and does not reduce prostaglandin levels. Multiple actions have been shown for sulindac sulfone, including inhibition of guanosine 3′,5′-cyclic monophosphate phosphodiesterase, activation of protein kinase G, and enhanced proteasomal degradation of β-catenin (15). Sulindac sulfone is clearly yet another multifunctional drug. Both sulindac sulfide and sulindac sulfone are effective inducers of apoptosis and effective preventive agents in animal models of intestinal neoplasia (14, 15, 18, 19).

The clinical results obtained with the combination of DFMO and sulindac are a ringing endorsement of a classic physiologic and pharmacologic approach to studying the prevention of disease. With their global, nonreductionistic orientation, Meyskens, Gerner and colleagues have focused on two processes that have long been known to be associated with the development of cancer: excessive synthesis of polyamines and enhanced inflammatory activity. They have not sought to define these activities in oversimplified, reductionistic terms but have rather chosen to use a combination of two unfashionable, but time-tested, drugs to control polyamine synthesis and inflammation. They have based their clinical study on extensive animal studies of chemoprevention of carcinogenesis, which supported their clinical selection of DFMO and sulindac (14, 20, 21). The totality of these basic animal studies, together with the clinical results reported here, provides an affirmation of the fundamental tenet of combination chemoprevention: to achieve therapeutic synergy while simultaneously lessening the undesirable toxicity that is often associated with the use of high doses of single drugs. It has taken more than 10 years to overcome many of the pitfalls of designing and implementing this landmark prevention trial of more than one drug, but with such persistence the clinical cancer research community now has a totally new paradigm for design of prevention trials in the future. Moreover, the magnitude of the results that have been obtained in this study also sets a new standard of efficacy for future investigations.

There are many important issues that still remain unsolved. Although impressive results have been obtained in suppression of recurrence of adenomas, it remains to be determined if the DFMO-sulindac combination will suppress occurrence of frank carcinoma. Does this drug combination have an effect on flat, nonpolypoid lesions in the colon? Can it be given safely for longer than 3 years? Would it be desirable to have some rest periods in which no drug is given at all? One wonders if the adverse effects that resulted from long-term continuous use of celecoxib and rofecoxib in chemoprevention trials might have been averted if drug-free rest periods had been an integral part of the protocol. The entire issue of optimal drug scheduling (continuous versus noncontinuous) remains an essentially unexplored issue in the clinical chemoprevention of cancer.

A final thought with respect to combination chemoprevention: This new study has opened the door to using more than one drug for cancer prevention. However, we should not confine these efforts to the use of only two drugs. The great advances that occurred a generation ago in the development of totally new chemotherapy for childhood leukemia and Hodgkin's disease were the result of the coordinated use of as many as four agents. The possibility to develop even safer and even more effective multiple-drug regimens for clinical chemoprevention of cancer should now be considered (22). It will require extensive modeling in animal studies and a major commitment from the clinical research community to undertake this unorthodox approach to cancer prevention. Moreover, there will be formidable regulatory and intellectual property problems to overcome. This exciting new study published in this new journal devoted to prevention of cancer provides a totally new perspective. We have reached an important milestone, and now we have a new standard of excellence as our goal.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Megan Padgett for editorial assistance with the manuscript.

References

1. Meyskens FL, McLaren CE, Pelot D, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res 2008;1. In press.
2. Sporn MB. Combination chemoprevention of cancer. Nature 1980;287:107–8.
3. Hong WK, Sporn MB. Recent advances in chemoprevention of cancer. Science 1997;278:1073–7.
4. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348:883–90.
5. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–9.
6. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885–95.
7. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355:873–84.
8. Baron JA, Sandler RS, Bresalier RS, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 2006;131:1674–82.
9. Meyskens FL, Jr., Emerson SS, Pelot D, et al. Dose de-escalation chemoprevention trial of

Published OnlineFirst April 14, 2008; DOI: 10.1158/1940-6207.CAPR-08-0049

α-difluoromethylornithine in patients with colon polyps. J Natl Cancer Inst 1994;86:1122–30.

10. Meyskens FL, Jr., Gerner EW, Emerson S, et al. Effect of α-difluoromethylornithine on rectal mucosal levels of polyamines in a randomized, double-blinded trial for colon cancer prevention. J Natl Cancer Inst 1998;90:1212–8.

11. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328:1313–6.

12. Gerner EW, Meyskens FL, Jr. Polyamines and cancer: old molecules, new understanding. Nat Rev Cancer 2004;4:781–92.

13. Pegg AE, Feith DJ. Polyamines and neoplastic growth. Biochem Soc Trans 2007;35:295–9.

14. Piazza GA, Alberts DS, Hixson LJ, et al. Sulindac sulfone inhibits azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. Cancer Res 1997;57:2909–15.

15. Thompson WJ, Piazza GA, Li H, et al. Exisulind induction of apoptosis involves guanosine 3′,5′-cyclic monophosphate phosphodiesterase inhibition, protein kinase G activation, and attenuated β-catenin. Cancer Res 2000;60:3338–42.

16. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001;286:954–9.

17. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.

18. Loveridge CJ, Macdonald AD, Thoms HC, Dunlop MG, Stark LA. The proapoptotic effects of sulindac, sulindac sulfone and indomethacin are mediated by nucleolar translocation of the RelA (p65) subunit of NF-κB. Oncogene 2007. In press.

19. Mahmoud NN, Boolbol SK, Dannenberg AJ, et al. The sulfide metabolite of sulindac prevents tumors and restores enterocyte apoptosis in a murine model of familial adenomatous polyposis. Carcinogenesis 1998;19:87–91.

20. Nigro ND, Bull AW, Boyd ME. Inhibition of intestinal carcinogenesis in rats: effect of difluoromethylornithine with piroxicam or fish oil. J Natl Cancer Inst 1986;77:1309–13.

21. Rao CV, Tokumo K, Rigotty J, Zang E, Kelloff G, Reddy BS. Chemoprevention of colon carcinogenesis by dietary administration of piroxicam, α-difluoromethylornithine, 16α-fluoro-5-androsten-17-one, and ellagic acid individually and in combination. Cancer Res 1991;51:4528–34.

22. Sporn MB. Dichotomies in cancer research: some suggestions for a new synthesis. Nat Clin Pract Oncol 2006;3:364–73.

AACR American Association for Cancer Research

Cancer Prevention Research

Clinical Prevention of Recurrence of Colorectal Adenomas by the Combination of Difluoromethylornithine and Sulindac: An Important Milestone

Michael B. Sporn and Waun Ki Hong

Cancer Prev Res 2008;1:9-11. Published OnlineFirst April 14, 2008.