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

Michael B. Sporn and Waun Ki Hong

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 non-steroidal 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 APC, KRAS, or MYC 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

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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 investment. 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 (13); DFMO is thus a classical multifunctional drug, and its overall action to suppress carcinogenesis cannot be explained in a simple reductionistic cartoon. The totality of these basic animal studies, 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.

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