Concomitant difluoromethylornithine/sulindac chemoprevention of colorectal adenomas: a major clinical advance

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Combining two drugs, i.e. difluoromethylornithine and sulindac, at low doses has been shown, for the first time, to provide both great efficacy and great safety for clinical colon cancer prevention.

Summary

In a randomised, placebo-controlled, double-blind clinical trial by **Meyskens et al**., the combination of difluoromethylornithine and sulindac has been shown to be strikingly effective for prevention of sporadic colorectal adenomas (**Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial** *Cancer Prev Res* 1:32–38). This concomitant use of two drugs to suppress the progression of preneoplastic lesions represents the first major clinical success of the application of the principle of 'combination chemoprevention'. Neither drug alone has previously had clinical utility at the low doses used in this trial. The combination of the two agents has provided synergistic efficacy in suppression of carcinogenesis, while minimising any undesirable adverse effects. This study should be the impetus for further clinical investigation of the use of multiple drugs for chemoprevention of cancer.

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As we have noted elsewhere,[1] the recent report[2] of the combined use of difluoromethylornithine (DFMO) and sulindac to prevent recurrence of colorectal adenomas in patients at high risk of such malignancies is a spectacular advance in the field of cancer treatment. The study by Meyskens and colleagues represents the first clinical validation of the concept of using more than one drug for effective chemoprevention, a theory that was first proposed many years ago.[3,4]

Chemoprevention is still a very controversial approach to the overall control of malignancy, particularly because of concerns about undesirable adverse effects of chemopreventive agents when given to asymptomatic patients over prolonged periods of time. In their clinical study, Meyskens and coauthors have clearly shown that unwanted adverse effects can be prevented by using the lowest possible doses of two drugs in a combination regimen, a strategy that can facilitate synergistic action between two agents while minimising their individual potential for toxicity. By contrast, conventional chemotherapy for treating advanced malignancy traditionally entails escalating the dosage of any therapeutic agent to its maximum tolerated level, and thus adverse effects are frequent. In the DFMO and sulindac chemoprevention study, the investigators used a brilliant, counterintuitive

'dose de-escalation' strategy. They first determined the lowest possible dose of either DFMO or sulindac that might provide a useful biological response, and then used these doses of the two drugs in combination. In previous clinical trials, neither DFMO nor sulindac has been particularly active or free of adverse effects as single agents.

The results obtained in the Meyskens et al. study are stunning. In this trial involving almost 300 patients, the drug combination reduced the overall incidence of adenoma recurrence by 70%, from 41% in the control population to 12% in the patients treated with the drug combination. Most striking were the effects of DFMO and sulindac on the number and severity of new adenomas. In this 36-month trial, only one patient in the treated group had multiple adenomas when examined at the final colonoscopy compared with 17 patients in the placebo control group. The severity of any adenomas that did recur was also markedly reduced by the DFMO and sulindac combination: 11 patients in the placebo group had adenomas classified as 'advanced', whereas such a lesion was found in only one patient in the combination therapy group. These preventive effects of the combination regimen were highly significant ($P<0.001$); such results have never been obtained in any previous clinical chemoprevention study.

An important point to note is that it is now clinically possible to minimise adverse effects of chemopreventive drugs by employing study designs that utilise dose de-escalation strategies, together with the combined use of multiple agents that will act synergistically. This approach was the aim of the original hypothesis of 'combination chemoprevention'. It is clear that dose escalation strategies that might be useful for clinical chemotherapy of advanced malignancy are not viable approaches to clinical chemoprevention of early, preneoplastic disease. In this regard, the unfortunate toxic events that have resulted from long-term administration of high doses of celecoxib[5] or rofecoxib[6] represent paradigms one wants to avoid in the future development of the entire field of chemoprevention of cancer.

So what is the ultimate significance of this new clinical advance in chemoprevention of preneoplastic lesions in the colon? The concept that the capacity to control the progression of preneoplastic lesions represents an ideal approach to treating cancer is hardly a new one. Indeed, at a conference on Early Lesions and the Development of Epithelial Cancer, held at the National Institutes of Health in Bethesda, MD, more than 30 years ago, this strategy was clearly enunciated. A final summary statement from the three-day international conference published in *Cancer Research* is as topical and relevant today as it was in 1975 when it was written.[7] It reads as follows:

> "The development of cancer in all of these organ sites is a prolonged process, which may take 20 years or more in humans to reach its invasive stages. Before invasive malignant disease occurs, various preneoplastic changes occur in all of the above organ sites. Although these preneoplastic changes have not been generally considered to be 'cancerous' (i.e. in the classical, clinical diagnostic sense of the term), they are definitely an integral part of the process of development of cancer. Because the prognosis for invasive malignant disease becomes worse as the stage of the disease increases, it is essential that more-intensive efforts be devoted to study of the disease process in its preneoplastic states.
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> "Greater effort must be devoted to development of new methods for detecting individuals at increased risk and to development of more accurate diagnostic markers, both of which will make possible a more meaningful definition of the various stages of preneoplasia and their relationship to invasive neoplasia. It is not yet clearly known at which stages the preneoplastic process is reversible and when it becomes irreversible. It is essential that a clearer definition of these stages be obtained. Greater effort also must be devoted to development of new methods of prevention of invasive cancer by application of treatment during those preneoplastic stages that have a very high likelihood of progressing toward invasive cancer. Further research on pharmacological, immunological, and surgical approaches to prevention and control of invasive disease while it is still in the preneoplastic state is thus critically needed."[7]

Unfortunately, more than 30 years later, the entire field of preneoplasia research still suffers from neglect, as more and more effort is devoted to seeking ultimate cures of advanced disease. Meyskens and colleagues' new clinical study on combination chemoprevention of colorectal adenomas with DFMO and sulindac represents a new advance that hopefully will help to redress the balance between cancer prevention and therapy and to redirect more effort toward control of early lesions. Such effort is critically needed.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

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