Title

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□□ *Commentary on Sabichi et al., p. 224*

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In general, progress in translating preclinical chemoprevention studies to the clinic has been limited to hormone-responsive tumors (breast, prostate), and to date, has not been widely adopted. Either the toxicities have been too great for general usage despite a definitive positive clinical trial (e.g., 13-cis-retinoic acid for suppressing oral leukoplakia or preventing secondary head and neck cancers) or the compounds have been inactive when subjected to a randomized trial, even in cases in which the phase II studies were promising. In the trial reported by Sabichi et al. in this issue (1), Fenretinide, an atypical retinoid identified as "promising" >25 years ago (2), and studied intensely in various preclinical models, failed to decrease the time-to-recurrence in patients with Ta, Ti, or Tis transitional cell carcinoma of the bladder. How come?

Although one can criticize many aspects of the exact design of this trial, most notably the inclusion of a cohort of patients previously treated with Bacillus Calmette-Guerin, which seriously confounds interpretation, this editorial will deal briefly with the more generic issue of "Why don't chemoprevention agents work in the clinic in nonhormonal cancers?" Translation of preclinical findings to benefit in the clinic needs to address a number of critical issues before being launched into a randomized trial (also see refs. 3, 4).

Is the animal model representative of the human disease and predictive? In general, we don't know, as studies correlating the results from preclinical animal models and clinical outcomes are seriously wanting. However, for bladder cancer, the answer would seem to be "No" as at least three agents difluoromethylornithine, Fenretinide, and Etretinate that were "promising" in preclinical models have failed to show benefit in definitive clinical trials. Perhaps, new models for bladder cancer prevention are needed. Or, perhaps it's the process of translation that is faulty. In the current trial, a safe, low dose of Fenretinide (200 mg/d) was chosen; indeed, no difference in unexpected toxicities was seen in the treatment arm compared with the placebo. However, it is likely that the dose was too low for several reasons: the serum levels achieved in patients in other studies at a similar dose was well below the dose at which Fenretinide has consistent apoptotic effects in cultures, a property generally believed from mechanistic considerations to be important for the activity of this compound. It would indeed have been surprising if the randomized trial had been positive based on this observation alone. However, a series of concerns about risk-benefit (retinoids, tamoxifen, cox-2 inhibitors) has contributed to a very conservative approach, in which the risk for underdosing frequently occurs in prevention trials.

For the future, is there any way to improve the chances, or put another way, what needs to be done before launching into a phase III trial? Here are a few suggestions and guidelines.

1. We need to examine more closely the validity of our preclinical animal models both as surrogates for the human disease and for their predictive ability.
2. If a marker has been chosen for monitoring based on a mechanistic observation (e.g., drug-produced apoptosis), it should be shown that its modulation really does correlate to its effect on tumors in the animal model (it is all too rare that investigators actually close this logical loop).
3. It needs to be shown that the drug or active metabolite is measurable in the tissue/organ (serum levels or surrogate tissues won't do) of interest in humans and/or better yet actually modulates a relevant marker in the organ of interest. For nonhormonal tissue, selecting an appropriate marker has been difficult. Unfortunately, to date, *no* universal biological marker has been validated as predictive in chemoprevention trials and the hard work of developing specific markers lies ahead. Whether solely achieving a relevant concentration of the active drug (or metabolite) in the organ of interest may, in some cases, be enough.
4. A major issue in developing chemoprevention drugs has been risk-benefit, a subject which has been widely discussed (5). An alternative approach to drug escalation schemas is to use a de-escalation dose design in which the dose of drug is gradually lowered in cohorts of patients to a level at which an effect on a relevant marker in the tissue/organ of interest can no longer be measured. If one is lucky, a dose may be achieved at which a biological effect is still seen but at which the threshold for significant clinical toxicity has not occurred. We have recently come to the 15-year end of a series of studies with difluoromethylornithine (6–8) which indicates that we have achieved this goal: reduction of colorectal adenomas without a difference in apparent clinical toxicities between placebo and treatment arms in a phase III trial.[1]

This editorialist sympathizes with the challenges that these investigators have had in completing this trial. For the future though, I think that a different and more rigorous approach needs to be undertaken despite the enormous difficulties in doing so. The recent approval of raloxifene for the prevention of breast cancer is an important object lesson because this drug was initially developed for noncancerous indications and therefore developed in a manner with close attention to concern about toxicities, risk-benefit, and risk-risk. There is an important lesson there.

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[1] Unpublished data, more to come.

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