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Chemoprevention, Risk Reduction, Therapeutic Prevention, or Preventive Therapy?

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In this issue of the Journal, Elmets et al. (1) report a randomized placebo-controlled trial of a moderate dose (ie, 200 mg twice daily) of celecoxib vs placebo in patients who have 10–40 actinic keratoses and Fitzpatrick sun-reactive skin types I, II, or III. The primary outcome was the number of new actinic keratoses after treatment. Although the number of actinic keratoses did not differ between the

two study arms, an exploratory analysis demonstrated a statistically significant time-dependent decrease in the number of all nonmelanoma skin cancers, including both basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). Adverse event rates, including serious and cardiovascular events, were indistinguishable between the study arms. What are we to make of these findings, and how, if at all, should they guide us toward a future for chemoprevention in the management of skin and other cancers?

Proof of principle for the pharmacological prevention of non-melanoma skin cancer in patients at moderate to high risk has been established over the past 25 years, and yet these interventions (retinoids, difluoromethylornithine, low-fat diet) have not been consistently adopted for patient care by the oncologic community (2–7). This phenomenon is not just an issue for nonmelanoma skin cancer but is also true in general for the prevention of three of the four major cancers in which chemoprevention has produced convincingly positive results [reviewed in (8)]. These include colorectal (adenomas), prostate (second malignancies), and breast (primary and second malignancies) cancers. Why have these interventions not been adopted? A recent commentary on this issue regarding the use of tamoxifen and raloxifene for the prevention of breast cancer has covered this issue well (9).

The results of the trial reported by Elmetts et al. highlight a central message that lesions at the late stage of cutaneous carcinogenesis were treated and prevented from progressing (from actinic keratosis to nonmelanoma skin cancer). No effect on progression of earlier lesions (ie, from photo-damaged skin to AK) was demonstrated. A thoughtful analysis of the issues related to early carcinogenesis offers a possible explanation (10), that is, the major driver(s) of early and late carcinogenesis may be different and, early in the process, more related to host cells than altered tumor genomics per se, and hence affected differentially by a chemoprevention drug. It is interesting that difluoromethylornithine, another chemoprevention compound, statistically significantly reduced development of BCC but had no effect on the incidence of new SCC (6), which is not surprising because the mechanisms involved in their underlying carcinogenic events, although perhaps partially shared, are clearly different (11,12).

Another striking feature of this trial is persistent suppression of nonmelanoma skin cancer even after the medication was stopped. A similar phenomenon has been demonstrated in trials of the prevention of second head and neck cancers with retinoids (13), in colorectal adenoma prevention trials with celecoxib (14), and, in the case of calcium, a further decrease in the number of adenomas (15) was observed after the medication was stopped. Recently, The Study of Tamoxifen and Raloxifene trial for the prevention of breast cancer demonstrated prolonged beneficial effects for both drugs (16). Long-term follow-up of the cohort in the current trial (1) and of patients enrolled in other preventive therapy trials will provide important information about the relative risk benefit of the agent, a key element of regulatory assessment. Because toxicity should diminish when the drug is discontinued while the benefit continues, the benefit–risk ratio increases markedly. This phenomenon should markedly and positively influence the regulatory decision of “go vs no go” for a new indication of an “old drug” or initial approval for a new agent.

This trial demonstrated no statistically significant differences in the occurrence of serious cardiovascular adverse events; how-

ever, such events would not necessarily have been expected because the dose was moderate, the trial was short, and the risk of cardiovascular toxic effects from COX-2 selective inhibitors seems to increase markedly only after about 12–18 months (17). What should be the next steps for the investigation of celecoxib given that this widely used drug clearly reduces the risk for progression of late-stage carcinogenesis in skin, colon, and probably other organ sites? We propose two major approaches: 1) lower the frequency of administration to once daily, considering that meta-analysis (17) suggests that the continuous suppressive effects of COX-2 inhibitors led to an increased cardiovascular risk, or 2) use a lower dose in combination with other proven compounds, a strategy that appears to be highly effective in the risk reduction of colorectal adenomas in patients at moderate risk for colorectal cancer (18).

The study by Elmetts et al. raises additional important issues for the field of “chemoprevention.” From a clinical viewpoint, we prefer to think of “chemoprevention” as risk reduction, preventive therapy, or therapeutic prevention, and we have a strong preference for risk reduction because this terminology fits into the nosology of the long-standing therapeutic paradigm for the management of cardiovascular diseases (19). For those who may object, we ask: “Are surgery or ablative interventions of precancers (and localized cancers) prevention or treatment?” Others have asked: “Should prophylactic surgery performed on individuals at high risk for a specific genetic disease be considered prevention or treatment?”

Notwithstanding the enormous regulatory challenges in bringing an agent, particularly one for cancer prevention (20), to market, the perception of the effectiveness of chemoprevention has also been marginalized by the use of the term “chemoprevention” by both the public and oncologic profession. Although “chemoprevention” is a revered term (21) and is still appropriate usage in the preclinical setting, it is time for the word to be retired from the clinic for it conveys the wrong message, that of toxic chemotherapy. The terminology needs to be updated and to enter the mainstream of medicine as risk reduction, and therapies for the reduction of risk factors for cancer should be integrated into the broader therapeutic paradigm for the management of cancer. This approach should reduce the number of patients who experience disease progression to overt advanced malignancy (9) and then require high-end testing with increasingly expensive technologies and only incrementally better tertiary treatment with very high price tags.

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Notes

F. L. Meyskens is co-founder of Cancer Prevention Pharmaceuticals, LLC; its major trials involve the drugs difluoromethylornithine (Eflornithine R) and sulindac (Clinoril R). C. E. McLaren has no potential conflict of interest to report.

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