Editorial

Cyclooxygenase Inhibition as a Target for Prevention of Tobacco-Related Cancers

Jay O. Boyle
Memorial Sloan Kettering Cancer Center, New York, New York

Despite the findings of the study by J. L. Mulshine *et al.* (1) in this issue demonstrating no apparent clinical benefit of topical ketorolac in oral leukoplakia, the hypothesis that cyclooxygenase (COX) inhibition may be beneficial in the prevention and treatment of tobacco-related malignancy and intraepithelial neoplasia remains extant. A great deal of preclinical data supports this hypothesis (1). The most appropriate clinical trial design, route of administration, selection of agent, target population, and study end points are not yet known.

The mechanisms of action of COX inhibitors in cancer treatment and prevention in humans are not fully known. Preclinical models have proposed antiangiogenesis, apoptosis, or growth inhibition as potential mechanisms depending on the model and agent (2). Altered carcinogen metabolism may also play a role. Although the proposed mechanisms are heterogeneous, the vast majority of studies shows significant efficacy in prevention of carcinogen-induced carcinoma in rodents. The molecular effects are likely to be mediated through reduction in prostaglandin concentrations but may be independent of COX enzyme inhibition. Several published reports show nonsteroidal anti-inflammatory drug use reduces colon cancer, and recently, Ibuprofen use was associated with decreased breast cancer (3).

Clinical trials for efficacy of agents for tobacco-related intraepithelial neoplasia frequently use the head and neck cancer model attributable to the known natural history of visible precancerous lesions (oral leukoplakia) and their accessibility. Efficacy in this model is presumed to correlate with cancer prevention. Patient selection is critical as the molecular profile of high-risk oral leukoplakia is being discovered. A majority (85%) of clinical leukoplakia contains no dysplasia but only hyperkeratosis. In general, studies do not include lesions without dysplasia or atypia, because hyperkeratosis or hyperplasia alone represents a risk of transformation $<5\%$ over 10 years. Efficacy of an agent on hyperplasia alone may not represent cancer prevention efficacy. Even dysplastic lesions in the United States show only a 30% progression rate over 8 years (4).

Further testing of oral leukoplakia for risk of transformation is available by ploidy or molecular analysis. Aneuploidy has been shown by Sudbo *et al.* (5) to be highly predictive of the risk of progression in a Northern European study. Ploidy was correlated with COX expression in oral leukoplakia (6). The group at MD Anderson noted loss of heterozygosity, trisomy 9, and p53 expression together correlated with risk of progression (7). Studying the highest risk lesions will provide the most insight into efficacy of agents, but this can severely inhibit accrual, because the high-risk lesions represent not $>20\%$ of all oral leukoplakia. In this study of Mulshine *et al.*, lesions were not selected for histological or molecular criteria; this limits the usefulness of the trial to some extent. In addition, COX-2 overexpression is variable among oral leukoplakia, and baseline quantification of COX-2 may be an important stratifying variable in future trials. In the future, stratifying lesions by molecular risk factors will be important. It is possible that only cytotoxic therapy can halt or reverse advanced precancerous lesions with fixed genetic changes, such as p53 mutation or aneuploidy.

COX-2 is capable of metabolizing aromatic hydrocarbon carcinogens to the ultimate DNA-binding diol-epoxide. Depending on the relative activity of other metabolizing enzymes, COX activity may lead to mutagenesis. Possibly, decreasing COX expression earlier in the carcinogenic process may be a mechanism of COX-related prevention. Other study designs are necessary to test this hypothesis.

The optimal COX-inhibiting agent, route of administration, and vehicle for cancer prevention are not known. Nonsteroidal anti-inflammatory drugs and ASA are known to prevent colon cancer in arthritis patients. Long-term toxicity of these agents caused by COX-1 inhibition is a major disadvantage to using these agents for decades in large populations. Therefore, COX-2-selective agents or topical routes for nonsteroidal anti-inflammatory drugs are logical. In the Mulshine study, it is possible that penetration of drug to the basal layer of proliferating cells may not have been achieved by this topical route or that other pharmacological activities of ketorolac are not favorable. The crevicular prostaglandin E_2 measurements that might have helped document COX inhibition were apparently not possible, which severely inhibits the interpretation of the study. It may be that systemic effects are necessary for adequate tissue levels or to adequately block lesion/host interactions, such as angiogenesis, because COX-2 inhibition is more effective than COX-1 in many preclinical studies. Perhaps COX-2-specific inhibition will prove more efficacious than nonsteroidal anti-inflammatory drugs. COX-independent effects may also prove to be important and suggest novel downstream targets. In addition, although the ketorolac vehicle used by Mulshine *et al.* showed higher than anticipated efficacy, one could challenge the use of 20% ethanol on the basis that ethanol contributes to carcinogenesis, especially in active smokers, and therefore should be avoided entirely. Ethanol, which is drying and an irritant, may have negated other beneficial effects of ketorolac. Inadequate dose or duration of exposure is also a possible explanation.

Currently, a multi-institutional randomized placebo controlled trial is being conducted with the COX-2 inhibitor cele-

Received 11/6/03; accepted 11/17/03.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Requests for reprints: Jay O. Boyle, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021. Phone: (212) 639-2906; E-mail: boylej@mskcc.org.

coxib for dysplastic oral leukoplakia. Other active trials are assessing effects in Barret's esophagus and bladder cancer. Perhaps these trials and others ongoing will shed additional light on the role of COX inhibition in prevention of tobacco-related cancer and treatment of intraepithelial neoplasia. It remains likely that COX inhibition will play an important role.

References

1. Mulshine, J. L., Atkinson, J. C., Greer, R. O., Papadimitrakopoulou, V. A., Van Waes, C., Rudy, S., Martin, J. W., Steinberg, S., Liewehr, D., Avis, I., Linnoila, R. I., Hewitt, S., Lippman, S. M., Frye, R., and Cavanaugh, P. F., Jr. Randomized double-blind, placebo-controlled, phase IIB trial of the cyclooxygenase inhibitor ketorolac as an oral rinse in oropharyngeal leukoplakia. Clin. Cancer Res., *10:* 1565–1573, 2004.

2. Lin, D. T., Subbaramaiah, K., Shah, J. P., Dannenberg, A. J., and Boyle, J. O. Cyclooxygenase-2: a novel molecular target for the prevention and treatment of head and neck cancer. Head Neck, *24:* 792–799, 2002.

3. Dannenberg, A. J., Altorki, N. K., Boyle, J. O., Dang, C., Howe, L. R., Weksler, B. B., and Subbaramaiah, K. Cyclo-oxygenase 2: a pharmacological target for the prevention of cancer. Lancet Oncol., *2:* 544–551, 2001.

4. Harris, R. E., Chlebowski, R. T., Jackson, R. D., Frid, D. J., Ascenseo, J. L., Anderson, G., Loar, A., Rodabough, R. J., White, E., and McTiernan, A. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res., *63:* 6096–6101, 2003.

5. Silverman, S., Jr., Gorsky, M., and Lozada, F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. Cancer (Phila.), *53:* 563–568, 1984.

6. Sudbo, J., Kildal, W., Risberg, B., Koppang, H. S., Danielsen, H. E., and Reith, A. DNA content as a prognostic marker in patients with oral leukoplakia. N. Engl. J. Med., *344:* 1270–1278, 2001.

7. Sudbo, J., Ristimaki, A., Sondresen, J. E., Kildal, W., Boysen, M., Koppang, H. S., Reith, A., Risberg, B., Nesland, J. M., and Bryne, M. Cyclooxygenase-2 (COX-2) expression in high-risk premalignant oral lesions. Oral Oncol., *39:* 497–505, 2003.

8. Lee, J. J., Hong, W. K., Hittelman, W. N., Mao, L., Lotan, R., Shin, D. M., Benner, S. E., Xu, X. C., Lee, J. S., Papadimitrakopoulou, V. M., Geyer, C., Perez, C., Martin, J. W., El-Naggar, A. K., and Lippman, S. M. Predicting cancer development in oral leukoplakia: 10 years of translational research. Clin. Cancer Res., *6:* 1702–1710, 2000.

Clinical Cancer Research

Cyclooxygenase Inhibition as a Target for Prevention of Tobacco-Related Cancers

Jay O. Boyle

Clin Cancer Res 2004;10:1557-1558.