Cyclo-oxygenase-2 inhibitors for chemoprevention of nonmelanoma skin cancer: Is there a role for these agents?

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Selective cyclo-oxygenase (COX)-2 inhibitors have been proposed as potentially useful agents in the chemoprevention of nonmelanoma skin cancer (NMSC).[1] Although COX-2 inhibitors are not without considerable risks, they may hold benefit for certain patient subgroups at risk for NMSC. In this article, we review studies examining the use of these agents in cancer prevention,[2-7] and offer suggestions for future investigations with oral and topical COX-2 inhibitors in the prevention of NMSC.

Abbreviations used:

AK:	actinic keratosis
BCC:	basal cell carcinoma
BCNS:	basal cell nevus syndrome
COX:	cyclo-oxygenase
FAP:	familial adenomatous polyposis
NMSC:	nonmelanoma skin cancer
XP:	xeroderma pigmentosum

WHAT ARE THE DATA SUGGESTING THAT COX-2 ANTAGONISTS CAN PREVENT NMSC?

The COX-2 enzyme is up-regulated in numerous types of premalignant and malignant neoplasms,[8-10] including NMSC,[11] and evidence from preclinical and epidemiologic studies of selective COX-2 inhibitors[3,12-16] and nonsteroidal anti-inflammatory drugs[12,17,18] has indicated that these agents may impact the development of NMSC. A double-blind placebo-controlled multicenter randomized trial of celecoxib, a selective oral COX-2 inhibitor, was conducted to evaluate its use in the chemoprevention of actinic keratoses (AK). The hypothesis was that agents capable of preventing AK might also be effective in preventing NMSC. A total of 240 patients with 10 to 40 AK were randomized to 200 mg of celecoxib twice daily or placebo. Although the incidence of AK was not reduced with this intervention, patients in the celecoxib arm developed fewer new NMSCs than those in the placebo arm (rate ratio 0.41, 95% confidence interval 0.23-0.72, $P = .002$) at 11 months after randomization.[19] Although this was not a primary or secondary end point, these data suggest that celecoxib could potentially reduce new NMSCs in patients with extensive actinic damage.

WHY WAS THE CONCEPT OF COX-2 INHIBITION FOR CHEMOPREVENTION OF NMSC SET ASIDE?

The rationale for the celecoxib study was based in part on chemoprevention trials in colon cancer. Various studies using oral COX-2 inhibitors for the prevention of colon cancer were initially performed in patients with familial adenomatous polyposis (FAP). These randomized, double-blind, placebo-controlled studies indicated that COX-2 inhibitors significantly reduced the extent of colorectal polyps in patients with FAP.[20,21] Subsequently, 3 prospective randomized, placebo-controlled, double-blind studies examined the use of a COX-2 inhibitor in preventing colon cancer in patients with history of colorectal adenomas.[22-24]

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Despite promising preliminary results that showed a significant risk reduction in recurrent adenomas, patients receiving rofecoxib and celecoxib experienced significant adverse effects, including a higher rate of thrombotic cardiovascular events.[22,23] These findings led to the termination of all 3 studies. Hence, the previously described randomized study of celecoxib in the prevention of NMSC also came to a premature close.[19]

CURRENT STATUS OF COX-2 INHIBITORS

The serious adverse effects reported in the colon cancer prevention studies led to a marked apprehension toward the use of COX-2 inhibitors. Specifically, rofecoxib was withdrawn from the market in 2004 due to increased risk for cardiovascular thrombotic events. Currently, celecoxib is still on the market, although a black-box warning remains because of the increased long-term risk for serious cardiovascular thrombotic events, myocardial infarction, and stroke.

In the major colorectal adenoma prevention trials, patients with baseline cardiovascular disease were more likely to experience complications,[25] and the mean or median age of all patients was older than 50 years.[22,23] Thus, younger patients with a genetic predisposition to certain cancers, such as those with FAP, may be better candidates for such chemoprevention, as shown in a phase-I study demonstrating safety of celecoxib in children ages 10 to 14 years with FAP. A longer duration trial is still in progress to further address these issues, as the long-term adverse effects of COX-2 inhibitors among children and younger adults are unknown.[26]

FUTURE DIRECTIONS: COULD THERE BE A ROLE FOR COX-2 INHIBITION IN NMSC?

Although concerns regarding safety should not be taken lightly, certain subsets of patients may derive a meaningful benefit from chemoprevention with oral COX-2 inhibitors that outweighs the potential risks. Such patients would be those who lack pre-existing cardiovascular disease or significant cardiovascular risk factors and are highly predisposed to NMSC (eg, basal cell nevus syndrome [BCNS], xeroderma pigmentosum [XP]).

Although mortality from NMSC may be relatively low in the US general population ($0.69/10^5/y$[27]), morbidity from NMSC in patients with BCNS and XP is quite considerable. Patients with XP have nearly a 10,000-fold increased risk to develop NMSC compared with the general population and half are given the diagnosis NMSC by 10 years of age.[28] Patients with BCNS are typically diagnosed early in the third decade, and often develop hundreds or thousands of basal cell carcinomas (BCCs) in their lifetime, commonly affecting the face.[29,30]

Recently, a double-blind, randomized, placebo-controlled study of celecoxib (200 mg twice daily for 24 months) in 60 patients with BCNS demonstrated a nonsignificant trend toward decreased tumor burden ($P = .069$).[31] In subjects with fewer than 15 BCCs at baseline there was a statistically significant improvement in number and burden of new BCCs ($P = .024$). Patients given placebo had a 50% yearly increase in BCC burden, whereas those treated with celecoxib experienced only a 20% yearly increase in burden of BCCs. The mean age of patients in this study was younger than 50 years, and no difference in adverse events was noted between the study arms.[31] These preliminary data are encouraging; thus, patients with BCNS may be a suitable group for a larger chemoprevention trial with COX-2 inhibitors. To our knowledge, there have been no published studies of oral COX-2 inhibitors in patients with XP. These patients may also represent a suitable population for a chemoprevention trial.

POTENTIAL FOR TOPICAL COX-2 INHIBITORS

Although oral COX-2 inhibitors may not be suitable for pervasive use because of the safety profile, topical COX-2 inhibitors may be a practical alternative with minimal systemic effects. Preclinical studies have shown promising results, and adverse effects are limited. A study of topical application of celecoxib in mice exposed to ultraviolet radiation led to a diminished inflammatory response in the skin.[32] In an additional murine study, topical celecoxib appeared to be successful in inhibiting the formation of new tumors in ultraviolet-irradiated mice and slowing the growth of established tumors although no statistical analyses were done to determine if observed differences were statistically significant.[33]

In the clinical setting there are no selective COX-2 inhibitors available for topical use. Diclofenac, a nonselective nonsteroidal anti-inflammatory drug that inhibits both COX-1 and COX-2, is available topically and has been successfully used in the treatment of AK.[34] In a study of 32 organ transplant recipients with 3 or more AK, patients were randomized to twice-daily treatment with 3% diclofenac in 2.5% hyaluronic acid or placebo for 16 weeks. Although no analysis of statistical significance was performed, lesion count increased by 17% in placebo group but decreased by 53% in the treatment group. No patients in the placebo arm cleared their AK, in contrast to 41% of diclofenac-treated patients who cleared all AK at 1-month