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Celecoxib Shows Potential Biological Effect as Chemopreventive for Lung Cancer

Researchers report that celecoxib (Celebrex) appears to decrease expression of a protein associated with cell proliferation (Ki-67) in current and former smokers, suggesting this drug could potentially serve as a chemopreventive agent for lung cancer.

This study included 212 current or former smokers who were randomized to one of four treatment arms over a six month interval: celecoxib for 3 months then placebo for 3 months; celecoxib for 6 months; placebo for 3 months then celecoxib for 3 months; or placebo for 6 months. The researchers found that Ki-67 expression was significantly decreased in patients treated with higher-dose celecoxib, but not lower-dose celecoxib or placebo.

Celecoxib is a cyclooxygenase-2 (COX-2) inhibitor and has been evaluated as a potential prevention agent for several types of cancer, but many such trials involving celecoxib have been halted because this class of drug was thought to increase the risk of cardiovascular disease. No cardiac problems were observed in patients in this study.

Abstract #1501

A randomized double-blind study of the biological effects of celecoxib as a chemopreventive agent in current and former smokers

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Background: Cyclooxygenase-2 (COX-2) is overexpressed in bronchial premalignancy and promotes tumor cell proliferation and survival. Bronchial premalignant lesions have enhanced cellular proliferation as measured by nuclear Ki-67 expression. In histologically normal bronchial epithelium, Ki-67 is detectable in basal and parabasal layers. Celecoxib (COX-2 inhibitor) may have activity in the bronchial epithelium of current and former smokers and this was tested by measuring Ki-67 in bronchial biopsy samples.

Methods: Patients (pts) with or without a prior cancer history were required to have at least a 20 pack-year smoking history and be disease-free for at least 6 months (mos). Pts were randomized into one of 4 treatments (3-mo intervals): celecoxib then placebo; celecoxib then celecoxib; placebo then celecoxib; placebo then placebo. Pts underwent bronchoscopy with biopsies at baseline, 3 and 6 mos. Celecoxib was administered at 200 mg bid (low dose, 81 pts), then changed to high-dose (400 mg bid, 123 pts). The study design had 80% power to detect a 1.2% difference in Ki-67 (celecoxib vs placebo) with 2 sided 5% level of significance. The primary endpoint was change in Ki-67 (baseline to 3 mos).

Results: From 11/01 to 9/06, 204 of 212 registered pts were randomized (median age 53 years, 106 males, 175 Caucasian, 162 current smokers, and 182 with no prior cancer history). 127 pts completed 3 mos and 104 completed 6 mos of treatment. 3 pts experienced one grade 3 toxicity. No cardiac toxicities were observed. Baseline Ki-67 expression in basal and parabasal layers was higher in current smokers than in former smokers ($p=.001$ and $p=.005$, respectively). Multivariable analyses revealed that basal layer Ki-67 expression decreased in current and former smokers treated with high-dose ($p=0.003$) but not low-dose ($p=0.88$) celecoxib (vs placebo).

Conclusions: This study is the first reported randomized trial of celecoxib in lung chemoprevention and demonstrates the possible importance of COX-2 inhibition in the prevention of lung cancer. Celecoxib was safe and tolerable and may have an effect of downregulating proliferation in the bronchial epithelium of current smokers. (Supported by grant 1P01 CA 091844, DOD W81XWH-04-0142, CA 16672)

Disclosures for research team: Nothing to disclose.