Could COX-2s stage a comeback in cancer?

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Hopes for a drug that could inhibit colorectal cancer took a knock last year due to revelations of serious side-effects. But a combination therapy may now offer a way forward.

A lifeline has been offered to the controversial cyclooxygenase-2 (COX-2) inhibitors that has the potential to salvage their use in colon cancer prevention. A late breakthrough session abstract (LB-4), presented at the 96th meeting of the American Association for Cancer Research (April 16–20) held in Anaheim, California, showed the combination of low doses of the non-steroidal anti-inflammatory drug Celebrex (celecoxib) and the cholesterol-lowering medication Lipitor (atorvastatin) inhibited 95% of tumours in rat animal models.

"When used together the drugs were most effective at doses substantially lower than when used alone," said the principal investigator Bandaru Reddy from Rutgers University, New Jersey. "This may be the most effective way to maximise the anti-cancer effects of the drugs, while also minimising toxicity or harmful side-effects."

COX-2 inhibitors – widely used as anti-inflammatory and pain-relief agents – have more recently shown promise in human trials and experimental animal models as chemopreventive agents against colon cancer. It is thought they exert their beneficial effects by targeting the COX-2 inflammation pathway leading to a reduction of eicosanoid production, which in turn influences cell proliferation, apoptosis and tumour growth. In addition, eicosanoids coordinate signalling between the cell origin (autocrine) and neighbouring cells (paracrine) by binding to transmembrane G-protein-coupled receptors. It is estimated that the COX-2 enzyme is overexpressed in 71–85% of colorectal cancers.

However, such potential applications have been brought into question by recent studies suggesting COX-2 inhibitors show cardiovascular toxicity. The first indication anything was amiss came with the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, published in November 2000 in the *New England Journal of Medicine* (343:1520–28). While demonstrating a reduced incidence of gastrointestinal lesions in the arm taking the COX-2 inhibitor Vioxx (rofecoxib), the study also showed a higher incidence of myocardial infarction for this group compared to those taking the standard dose of the non-steroidal anti-inflammatory drug Naproxen (1000 mg a day). As this study lacked a placebo group, it was unclear whether the effect was due to an increased cardiovascular risk with Vioxx, or the protective effect of Naproxen, or whether it was merely a chance finding.

Two studies published in the March 17, 2005 issue of the *New England Journal of Medicine*, reviewing the cardiovascular effects of two COX-2 inhibitors have helped clarify the situation.

In the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, by Robert Bresalier and colleagues from the Anderson Cancer Center, University of Texas (NEJM 352:1092–1102), 2,586 patients with a history of colo-rectal adenomas underwent randomisation to receive 25 mg Vioxx daily or placebo. The results showed that a total of 46 patients in the rofecoxib group had a confirmed thrombotic event during 3,059 patient-years of follow-up (1.5 events per 100 patient-years) as compared with 26 patients in the placebo group during 3,327 patient-years of follow-up (0.78 events per 100 patient-years).

In the Adenoma Prevention with Celecoxib (APC) study, by Scott Solomon and colleagues from Harvard Medical School, Boston (NEJM 352:1071–80), 2,035 patients with a history of colorectal

Bandaru Reddy: Extrapolating to humans, celecoxib used in combination inhibits cancer at one sixth the dose of previous studies

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neoplasia were enrolled in a trial comparing two doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal cancer. Results showed that the composite cardiovascular end point of death from cardiovascular causes (myocardial infarction, stroke or heart failure) was reached in 7 out of 679 patients in the placebo group (1%); 16 out of 685 patients receiving 200 mg celeboxib twice daily (2.3%) and 23 out of 671 patients receiving 400 mg celecoxib twice daily (3.4%). "Since both these studies are in the preventative setting, the clinical implication is that the risks may outweigh any benefits," commented Andrea Decensi, of the division of chemoprevention at the European Institute of Oncology, Milan.

In the latest study, Reddy and colleagues decided to test their hypothesis that the combination of more than one drug targeting more than one gene used at very low doses would synergistically increase the cancer prevention efficacy, while at the same time lessening toxicity.

"In addition to COX-2 inhibitors we decided to focus on statins, since observational studies have shown that colon cancer rates are suppressed in patients taking these drugs," said Reddy.

He explained that by reducing levels of cholesterol, statins also act to inhibit the synthesis of bile acids, which are modified by bacteria in the colon into secondary bile acids, which include two strong tumour promoters. In addition, statins also inhibit the production of isoprenoids including geranyl pyrophosphate and geranylgeranyl pyrophosphate, which can activate some oncogenes, such as RAS. Statins may also enhance apoptosis.

In Reddy's study, rats at the age of seven weeks were given injections of the colon cancer tumour promoter azoxymethane (AOM) for two weeks, and then randomised to four groups. The first received 600 parts-per-million (ppm) celecoxib, the second 150 ppm Lipitor, the third 300 ppm celecoxib added to 100 ppm Lipitor, while the fourth group acted as a control. Results showed that, by itself, celecoxib at 600 ppm reduced the incidence, as well as the number of colon adenocarcinoma, by 80%; Lipitor alone, at 150 ppm, reduced tumour incidence by 31–41%, while the combination of 300 ppm celecoxib and 100 ppm Lipitor reduced invasive and non-invasive adenocarcinomas by 95%.

"If you extrapolate this to the human situation, we're using celecoxib at the equivalent of 120 mg/day, compared to 800 mg/day in the NEJM studies. It shows that we can get really effective cancer inhibition by using approximately one sixth of the dose," said Reddy.

Decensi commented: "It's plausible that these lower doses may not have so many adverse cardiovascular effects, but confirmation studies will need to be performed before we can take these observations further in a clinical setting."

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