COX-2 Inhibitor Therapy: Potential Relevance as Cancer Treatment?

We'll break from brain metastases for a while to talk about another potential avenue of targeted therapy in lung cancer: the cyclo-oxygenase, or COX, pathway.

Cyclo-oxygenase (COX) inhibition has been studied as a potential mechanism for inhibiting cancer over the past few years, and recently some early clinical trial results have looked promising and generated a great deal of enthusiasm. A central component of the arachadonic acid pathway (complicated, and not on the quiz, so don’t worry about it unless very motivated), COX is an enzyme found in two common forms, COX-1 and COX-2. COX-1 is constitutively expressed, which means it is present routinely in normal cells and plays a part in many routine cellular functions, among them helping to maintain the gastrointestinal (GI) mucosa. In contrast, COX-2 is an inducible enzyme, meaning that it is expressed selectively in the setting of signals that trigger inflammation as well as cancer development. Non-steroidal anti-inflammatory drugs (NSAIDs), your basic naproxen or ibuprofen, block both COX-1 and COX-2, and they can effectively reduce pain in the setting of inflammation, which is why they are taken for back pain and muscle aches, etc. Unfortunately, they can block some of the normal activities of platelets, which are important in clotting when you need to, and they can harm the stomach lining and lead to ulcers (remember that COX-1 helps maintain the stomach lining) and GI bleeding, which is uncommon but definitely seen with NSAIDs. COX-2 inhibitors, in contrast, have the potential to block inflammatory effects without the detrimental effects on platelet function or stomach lining. Here’s a pretty detailed diagram:

![Cyclo-oxygenase (COX) Pathways](https://via.placeholder.com/150)

(click to enlarge)

As you probably know from watching the news in the last few years, COX-2 inhibitors don’t appear to be toxicity-free, either. Rofecoxib (Vioxx) was taken off of the US market after initial FDA approval based on findings of increased cardiac events (summarized here), and there have also been reports about similar increases in cardiovascular events among people who received celecoxib (Celebrex) (abstract here).

Why are we talking about medicines for musculoskeletal pain here? Because COX-2 may be relevant in the development of, and treatment of, cancer. For starters, I mentioned that it isn’t seen in normal tissues, but it’s present on many different types of cancers, including NSCLC.
Lab studies also show that COX-2 expression leads to several advantages for tumor cells, including promoting angiogenesis (increased blood supply to the tumor), inhibiting apoptosis (programmed cell death that could otherwise auto-destruct a dysfunctional cell), and increasing adhesion to the extracellular matrix (which promotes invasion and metastatic tumor spread). These are all bad things, and in fact, blocking COX-2 can have anti-angiogenic properties, reverses growth of pre-malignant colon polyps that otherwise grow to become colon cancer in patients with a familial high-risk syndrome (abstract here), and inhibits tumor cell growth in many test tube and animal models.

In actual humans, it also appears that high COX-2 expression of NSCLC tumors is associated with worse outcomes. One early trial from Japan (abstract here) looked at 130 lung adenocarcinomas and found that survival was better for the patients with low COX-2 expression, and this result was particularly seen for patients with stage I tumors:

Another study from the US by a brilliant young oncologist named West (abstract here) revealed that stage I NSCLC tumors that recurred were significantly more likely to have high COX-2 expression than the stage I tumors that did not recur, and that overall stage I tumors were less likely to have high COX-2 expression than stage IV tumors:

And while not statistically significant with the small numbers tested (total of 28 stage IV tumors), the median survival for stage IV patients who had tumors without COX-2 expression was 19 months, vs. 10.7 months for those with COX-2 positive tumors. And other groups have
also found this association of better survival in patients with tumors showing low COX-2 expression (abstract here, another here):

Fair to say, then, that COX-2 expression is associated with worse outcomes in cancer, particularly lung cancer, and that we've seen that celebrex can reverse precancerous polyps that lead to colon cancer. But do celebrex or other COX-2 inhibitors provide a treatment benefit in lung cancer? We'll examine studies combining celebrex with both chemo and EGFR inhibitor therapies next.