COX-2 targeting in cancer: a new beginning?

Cyclo-oxygenase-2 (COX-2), the inducible enzyme catalyzing the rate-limiting step in the conversion of arachidonic acid into eicosanoids, is overexpressed in a wide variety of malignancies and associates with poor prognostic features [1]. Consequently, selective COX-2 inhibitors have been explored as therapeutic or chemopreventive agents in different settings; however, initial enthusiasm was tempered by reports of substantial gastrointestinal toxicity as well as of increased cardiovascular risk, mostly coming from postmarketing use as anti-inflammatory drugs and Cancer Research Campaign (UK) chemoprevention trials and eventually resulting in the withdrawal of rofecoxib from the market [2].

Recently, Edelman et al. [3] reported the results of a phase II study randomly combining standard chemotherapy with celecoxib or zileuton, alone or in combination, as first-line treatment of advanced non-small cell lung cancer (NSCLC). While the study failed to demonstrate a significant benefit for either agent in unselected NSCLC patients, it did report a thought-provoking result: COX-2 overexpression had, indeed, a significantly negative prognostic impact, that was overcome by the addition of celecoxib to chemotherapy.

In line with the results reported by Edelman and coauthors in NSCLC, we recently reported the results of a phase II study in advanced breast cancer patients, who received celecoxib in combination with capecitabine [4]: assessment of COX-2 expression in the small cohort of patients with available tumor tissue demonstrated a significantly better outcome for those

whose tumors overexpressed COX-2. We believe that such recently emerged data should prompt a profound re-evaluation of both the prognostic and the predictive potential of COX-2 expression in different cancers and should renew the interest of the oncology community towards COX-2 inhibition in combination with chemotherapy as a potentially effective and relatively inexpensive therapeutic strategy for appropriately selected patients. Indeed, another interesting finding emerging from recent studies in breast and pancreatic [4, 5] cancers is that celecoxib at the commonly used dose of 400–800 mg/day administered for a limited period of time to advanced cancer patients is well tolerated, does not cause excess cardiotoxicity, and, at least when combined with fluoropyrimidines, may even decrease certain chemotherapy-related toxic effects [4].

Is this the beginning of a new era for COX-2-targeted agents in cancer therapy? As with all 'targeted' therapies, the Holy Grail is to target COX-2-directed agents to the right patient populations. In that respect, evidence is now there to indicate the way: immunohistochemical detection of COX-2 expression is a relatively simple, straightforward, and widely available technique; its application to carefully designed and controlled randomized clinical trials should help us confirming or discarding the hypothesis that COX-2-targeted agents, such as celecoxib, may constitute a useful adjunct to our therapeutic armamentarium against cancer.

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doi:10.1093/annonc/mdn286
Published online 13 May 2008