Editorial

COX-2 inhibitors in NSCLC: never-ending story or misplaced?

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Comment on: Edelman MJ, Wang X, Hodgson L, *et al.* Phase III Randomized, Placebo-Controlled, Double-Blind Trial of Celecoxib in Addition to Standard Chemotherapy for Advanced Non-Small-Cell Lung Cancer With Cyclooxygenase-2 Overexpression: CALGB 30801 (Alliance). J Clin Oncol 2017;35:2184-92.

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The relationship between inflammation and cancer is not a new concept (1-4). In the 19th century, professor Virchow hypothesized that chronic inflammation could be crucial in the origin of cancer process, mainly due to maintained tissue injury causing enhancement of cell proliferation. Today, there is an established and growing knowledge on the complex mechanistic pathways underlying cancer-related inflammation, involving an environment rich in inflammatory cells, growth factors and activated stroma. One way to link chronic inflammation with cancer is through the intrinsic inflammatory pathway, in which genetic alterations that induce malignant transformation also produce a cancer-promoting microenvironment. The extrinsic one concerns the inflammatory conditions predisposing to cancer development. The convergence of both pathways activates transcription factors, coordinating the production of inflammatory mediators and ultimately generating a cancer-related inflammatory microenvironment (5).

The family of cyclooxygenase (COX) enzymes catalyze the two rate-limiting step of prostaglandin biosynthesis from arachidonic acid (6). The arachidonic acid is released from the plasma membrane by phospholipase A2 and through COX activity it is converted to prostaglandin G_2 (PGG_2). Secondly, a peroxidase reaction performs the conversion of PGG_2 to prostaglandin H_2 (PGH_2). At this point, PGH_2 is an unstable endoperoxide that is converted by specific synthases to PGs of the E_2, D_2, $F_{2\alpha}$ series and also to prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) (7).

Overexpression of cyclooxygenase-2 (COX-2) has been detected in the most frequent tumours such as non-small cell lung cancer (NSCLC) (8-10). COX-2 expression has a crucial role in complex process such as angiogenesis, invasion and immune suppression. It is also found to be associated with an increased production of prostaglandin E_2 (PGE_2) that plays a role in the carcinogenesis of NSCLC. Selective COX-2 inhibitors have shown inhibition of cell proliferation in NSCLC cell lines and in xenograft models, but also enhancement of antitumor activity when combined with conventional anticancer agents *in vitro* and *in vivo*.

The selective COX-2 inhibitors (with high specificity) act competitively on the activating domain of COX-2 and in the last decades have been a constant focus of clinical research.

Two decades ago, it was first documented that 70% to 90% of lung adenocarcinoma and around 70% of atypical adenomatous hyperplasias (premalignant lesions) exhibited high expression of COX-2 by immunohistochemistry (IHC) (8-10).

Thereafter, a significant relationship (P=0.034) between overexpression of COX-2 and shortened survival in a cohort of resected lung adenocarcinoma patients with stage I disease was reported (11). COX-2 mRNA expression was subsequently evaluated in a larger retrospective cohort of 160 patients with resected early stage NSCLC (12). The strength of COX-2 expression (strongly positive, intermediately positive, weakly positive and negative) was associated with worse overall survival rate.

A meta-analysis including nineteen heterogeneous

and retrospective trials (of a total of 2,651 patients with NSCLC) was published highlighting that COX-2 overexpression was associated with poor survival (HR 1.86; 95% CI: 1.58–2.20, P=0.017 for heterogeneity) (13).

With this hopeful background, using the COX enzymatic family as the cornerstone, COX-2 inhibitors were evaluated in clinical trials, as promising target agents in the advanced setting of NSCLC.

The factorial phase III randomized GECO trial for advanced NSCLC in first-line treatment was aimed to assess the addition of rofecoxib to standard treatment (cisplatin plus gemcitabine); but unfortunately, rofecoxib did not prolong overall survival (14). At the same time, the data of the phase II GALGB trial 30203 in advanced NSCLC to test celecoxib and zileuton added to first line treatment were published (15). Although the study failed to demonstrate differences on survival, a prospectively predefined subset analysis suggested an advantage of celecoxib plus chemotherapy for those patients with moderate to high COX-2 expression by IHC. Other two randomized phase III trials were published using COX-2 inhibitors used in combination with first line chemotherapy (16,17). In the framework of the two studies, a survival benefit as primary endpoint was not met. Furthermore, in the NVALT-4 study and in spite of not being a study selected only for population with high COX-2 expression, subset biomarker study did not demonstrate increased survival in those patients with increased COX-2 expression treated with celecoxib (16).

In the article accompanying this editorial, Edelman *et al.* reported the data of a randomized, placebo-controlled, double-blind phase III CALGB 30801 trial of celecoxib in addition to first line standard chemotherapy for advanced NSCLC and prospectively selected with moderate to high COX-2 expression by IHC (18). On the basis of data from the CALGB 30203 phase II study conducted by the same investigators indicating possible use of COX-2 overexpression in patients with advanced NSCLC as a possible prognostic or predictive biomarker of response for treatment with COX-2 inhibitors, the prospective confirmatory phase III trial CALGB 30801 was designed. In this trial, 529 patients registered were screened for COX-2 expression (with the same IHC index method previously used, defined as the product of the intensity and percentage of cells staining) and with a COX-2 index ≥2 percentage of 80% (422 patients); although only 312 patients with COX-2 overexpression were randomized to chemotherapy plus celecoxib 400 mg twice per day or chemotherapy plus placebo. Unfortunately, the study was halted due to futility; there were no significant differences between both groups (HR 1.046 for COX-2 ≥4). The study failed to demonstrate an improvement in survival with the addition of celecoxib in patients with advanced NSCLC selected for COX-2 overexpression by IHC.

In that sense, it is worth highlighting the data of meta-analysis of nine randomized clinical trials (comprising 1,679 patients) to assess the effect of COX-2 inhibitors for patients with NSCLC (19). Meta-analysis concluded that COX-2 inhibitors had no impact on survival in advanced NSCLC setting,

Another question that needs to be answered is how do COX-2 inhibitors remain in lung cancer? It is perhaps at COX-2 inhibitors are misplaced and we have a good preliminary preclinical data to relocate them in another scenario. COX-2 overexpression is associated with an increased production of PGE_2 that plays a role in the carcinogenesis of lung cancer and overexpression of COX-2 are detected in about seventy percent of atypical adenomatous hyperplasias who play an important bridging role as precancerous lesions. COX-2 and its derivatives PGE_2, TXA_2 and PGI_2 have well-known roles in cancer but also they are associated with cigarette smoking (20). Approximate 80% of lung cancers are attributed to cigarette smoking and smokers tended to have more COX-2 expression than non-smokers. Cigarette smoke exposure (tobacco carcinogens as nicotine and NNK) can induce COX-2 expression and lead to PGE_2 release from alveolar macrophages and lung dendritic cells. Additionally, carcinogen products stimulating the production of PGE_2 may facilitate the pro-inflammatory environment, a suitable scenario for the development of lung tumours.

If we take this fact and associate it with the Wingless-type protein (Wnt) signaling pathway through β-catenin that may play a role in maintaining cancer stem cells population and there is evidence that this Wnt pathway is important in the development of lung cancer. Wnt pathway could be important in lung cancer tumorigenesis and prognosis. β-catenin was expressed in more than ninety percent of resected squamous-NSCLC samples and in fifty percent of non-squamous NSCLC samples (21). Besides, in cultured respiratory epithelium, tobacco carcinogens upregulated Wnt signaling (22). Wnt pathway is complex and there could be possible links with other pathways. There are preclinical data that sulindac (NSAID) suppressed β-catenin expression in lung cancer cells, downregulated transcriptional targets of β-catenin and inhibited proliferation (23). There is growing evidence

to support that induction of apoptosis contributes to the anti-neoplastic activity of celecoxib, as it induces apoptosis independently from its COX-2 inhibitory action via a mitochondrial apoptosis pathway.

Due to the strong molecular basis to support the role of COX-2 inhibition in NSCLC, we believe that further efforts should be made focusing the approach on a less advanced stage of the disease. The potential role of celecoxib as a preventive agent in high-risk population for lung cancer (high tobacco exposure, radon exposure, chronic obstructive pulmonary disease, familiar history) should be analyzed and evaluated in randomized clinical trials.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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