Editorial

Revisiting the role of COX-2 inhibitor for non-small cell lung cancer

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Abstract: Accumulating preclinical and clinical studies have shown that cyclooxygenase-2 (COX-2) inhibitor has some efficacy for non-small cell lung cancer (NSCLC). However, two phase III clinical trials using COX-2 inhibitor in combination with platinum-based chemotherapy showed no survival benefit for "unselected" patients with advanced NSCLC. Thus, exploratory analyses of the association between biomarker and clinical outcome of NSCLC patients treated with COX-2 inhibitors have been warranted. A report by Edelman recently published in the *Journal of Clinical Oncology* demonstrated the results of a prospective randomized trial using a combination of chemotherapy (docetaxel or pemetrexed) and either COX-2 inhibitor or a placebo for patients with advanced NSCLC. The remarkable point of this study was that it adopted the eligible criteria requiring decreased urinary levels of prostaglandin E metabolite (PGE-M) after administration of COX-2 inhibitor in a run-in period, as a possible predictive marker for the COX-2 inhibitor. The primary endpoint was progression-free survival (PFS). However, no improvement in PFS was observed between the patients treated with COX-2 inhibitor and those with placebo. A number of efforts from various investigators, including this report, have failed to demonstrate the meaningful clinical effect of COX-2 inhibitor for NSCLC. Is COX-2 inhibitor useless anymore? Here, we address the "difficult" character of this COX-2 inhibitor from various viewpoints and discuss potential future strategy using this drug.

Keywords: Chemotherapy; clinical trial; cyclooxygenase-2 (COX-2); non-small cell lung cancer (NSCLC)

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Cyclooxygenase-2 (COX-2), the enzyme that converts arachidonic acid to prostaglandins (PGs), is expressed in many solid tumors and is associated with carcinogenesis, tumor proliferation, infiltration, metastasis, angiogenesis, as well as tumor resistance to anti-cancer drugs (1). In lung cancer cells, COX-2, which is overexpressed particularly in adenocarcinoma, is considered to be a negative predictive factor in the survival of the subpopulation (2). Preclinical and clinical studies have shown that COX-2 inhibitor has some efficacy for non-small cell lung cancer (NSCLC). Based on these findings, two randomized phase III trials using COX-2 inhibitor in combination with chemotherapy were conducted. However, the primary endpoint, the overall survival (OS) in either trial, was not met (3,4). One of the studies (3) demonstrated no statistical difference regarding OS between the NSCLC patients whose tumors were positive and negative for COX-2 expression by immunohistochemistry, although the results were from a retrospective analysis. Since then, enthusiasm for treatment using COX-2 inhibitors for patients with NSCLC has been tempered. In such situations, new approaches of the use of COX-2 inhibitors or other optimal selections of patients are warranted.

The discovery of epidermal growth factor receptor mutation, anaplastic lymphoma kinase gene rearrangement, and subsequent successful gene-directed therapy, have led us to reconsider the importance of the molecular-oriented patient selection design of prospective clinical trials and the development of companion diagnostics. In the field of COX-2 inhibitor for NSCLC, various investigators have sought to find the association of specific molecules and the response to COX-2 inhibitor. Edelman's group has made tremendous efforts to develop a new strategy using COX-2 inhibitor, and has recently released a paper published

in the *Journal of Clinical Oncology* (5). They conducted a prospective randomized, placebo-controlled, multicenter phase II trial of apricoxib, a COX-2 inhibitor with potentially more preclinical activity than celecoxib, with either pemetrexed or docetaxel, as a second-line therapy for advanced NSCLC patients. The patients eligible for this study had ≥50% decrease of urinary levels of prostaglandin E metabolite (PGE-M: 11α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid) after an open-label 5-day administration of apricoxib, in a run-in period. The primary endpoint was progression-free survival (PFS). The rationale of the selection of this biomarker analysis was following two studies: one was Csiki's report (6), which had demonstrated results of a prospective phase II study using celecoxib in combination with docetaxel. In Csiki's study, patients with ≥72% decline in urinary PGE-M levels experienced longer survival compared to those with <72% decline-to-no change, or those with an increase in PGE-M (14.8, 6.3, and 5.0 months, respectively). In a multivariate model accounting for sex, smoking history, and histology, changes in PGE-M had a strong association with OS (odds ratio: 1.905; 95% CI: 1.192-3.044; P=0.007). The other study was Reckamp's phase I study (7), which had used a combination of apricoxib with erlotinib, and had showed potentiation of urinary levels of PGE-M decline for disease stabilization in patients with advanced NSCLC. A subsequent phase II trial (8), using the same eligible criteria in terms of ≥50% decrease in urinary levels of PGE-M from baseline as Edelman's paper, showed a significant improvement in disease control rate, time to progression, and OS for patients who were younger than 65 years of age. Despite these promising results, Edelman's study, which accrued patients with higher decline in urinary PGE-M levels from baseline, did not recapitulate the statistical differences between patients treated with COX-2 inhibitor and those treated with placebo in PFS. This discrepancy in the results might have been derived for several reasons: (I) the preferable results from the rational studies were derived from a subgroup analysis with smaller sample size; (II) difference of distribution of age, cut-off value of declined urinary levels of PGE-M from baseline, combination drugs with COX-2 inhibitor, and COX-2 inhibitor itself might have affected the clinical outcome; (III) COX-2 expression might correlate with the response to COX-2 inhibitors in several previous studies. Urinary PGE-M correlates with intratumoral prostaglandin E2 (PGE2) levels (6), however, baseline urinary levels in a paper by Csiki's (6), did not correlate with the response to COX-2 inhibitor. The reliability of PGE-M urinary levels and the meaning of declined PGE-M urinary levels are still to be discussed.

Interestingly, in Edelman's study (5), there was a trend of adverse interactions with docetaxel plus apricoxib compared with pemetrexed plus apricoxib. Patients who received docetaxel plus apricoxib had a numerically inferior median PFS to those treated with docetaxel plus placebo (hazard ratio: 1.62; P=0.18). Taxanes have been documented to stimulate COX-2 expression followed by increased PGE2 production (9); thereby a complementary and additive or synergistic effect with a COX-2 inhibitor was expected. However, the combination showed negative results in Edelman's study. Taxanes-driven augmentation of COX-2 expression, which correlates with survival, might diminish the effect of COX-2 inhibitors.

Is COX-2 inhibitor no longer regarded effective for patients with advanced NSCLC? How can we maximize the effect of COX-2 inhibitor and deliver good news for patients with NSCLC? Several approaches need to be considered.

Firstly, there have been no prospective phase III trials with the design of COX-2 inhibitor or placebo used only for COX-2-positive patients with NSCLC. Groen *et al.* (3) failed to demonstrate the relationship between COX-2 positivity, and PFS as well as OS. However, this was a retrospective subgroup analysis of a smaller sample size. A phase II trial (10), which was published in 2008 in the *Journal of Clinical Oncology*, also by Edelman *et al.*, demonstrated that a predefined analysis suggested survival advantage with COX-2 inhibitor and chemotherapy in patients with moderate to high COX-2 expression. Another group conducted a phase II trial using COX-2 inhibitor combined with platinum-based chemotherapy for 44 previously untreated patients of advanced NSCLC with COX-2 positive confirmed by immunohistochemistry. They demonstrated promising results, in which the median PFS and OS were 6 months and 18 months, respectively (11). Before attempting the phase III clinical trials using the design, confirmation of repeated positive results of a study with a smaller number of patients using optimal antibody for COX-2 and the establishment of effective laboratory technique should be warranted.

Secondly, our results (12) and those of the previous phase II trials indicated that patients who do not express COX-2 may have worse outcomes when treated with COX-2 inhibitor. Inhibition of COX-2 is reported to result in an imbalance between anti- and pro-thrombotic factors, with a predominance of thromboxane (TX) A2 at the expense of prostacyclin, which triggers a series of cardiovascular complications (13). TXA2-TXA2 receptor

signaling facilitates tumor colonization through interaction of tumor cells with platelets and endothelial cells in the tumor microenvironment (14). TXA2 is also shown to enhance tumor metastasis (15). Therefore, it is speculated that by inhibition of COX-2, the COX-1 pathway might be dominant in normal cells, thereby assisting tumor growth in COX-2-negative cell populations. The individual analysis of the COX-1/COX-2 balance of each tumor and the surrounding microenvironment may be important. Other investigators reported that celecoxib treatment induced epithelial-mesenchymal transition, which promoted cell invasion and rendered cells resistant to chemotherapy (16). We should be aware that these negative effects may also obscure the positive effects in COX-2-expressing patients.

Thirdly, examination of the genetic and epigenetic background of a tumor may be important in finding patients who are benefited by COX-2 inhibitor. Although genes in the COX pathway are seldom mutated in cancer cells, epigenetic alterations such as DNA methylation are recurrent events, and are associated with longer recurrence times and better OS, as demonstrated in gastric cancer (17). Kraus *et al*. recently showed that the profile of genetic polymorphisms detected from patients' blood was significantly associated with colorectal adenoma recurrence and toxicity in a COX-2 trial (18). Further investigation, however, is required for the association of genetic and epigenetic deregulation of the COX pathway with clinical outcome in lung cancer.

Next, immunological approach could be another option. A recent immune checkpoint modulator opened a new era for the treatment of patients with malignancy. Previous studies demonstrated that COX-2 augments immunosuppressive status in and around the tumor, thus a combination of COX-2 inhibitor with immune checkpoint modulators such as antagonistic programmed death 1 (PD-1) antibody or programmed death-ligand 1 (PD-L1) antibody may be promising. Indeed, a preclinical study examined mammary tumor onset in ErbB2 transgenic mice that were deficient in mammary epithelial cell COX-2 compared to wild type (19). The COX-2 knockout model showed late delay of tumor onset containing more CD4+ T cells and CD8+ cytotoxic T lymphocytes along with decreased expression of PD-1 and PD-L1 in the tumor. Another preclinical study suggested that agonistic anti-CD40 antibody therapy in combination with celecoxib induced marked anti-glioma effects by promotion of type-1 immunity in myeloid cells and T cells (20).

Lastly, a COX-2 independent mechanism should be considered. Increased p27 by a COX-2 inhibitor is attributed to COX-2 independent mechanisms of G0/G1 block of NSCLC cells (21). Thus, p27 expression may be another predictive factor of COX-2 inhibitor response. We conducted a phase II trial with preplanned exploratory analysis of p27 and COX-2 expression levels in tumors so as to find the correlation between the molecules and the clinical outcome of the combined treatment (12). There was a trend of correlations between the level of COX-2 expression and overall response rate, while p27 status did not show any statistical correlation. Nonetheless, there are still several molecules to decrease cell proliferation in a COX-2 independent manner that should be further investigated. A recent publication by Chen *et al*. demonstrated that COX-2 inhibitor reduced an influx of cisplatin in gastric cancer cells, and thereby antagonized cisplatin-induced cytotoxicity and apoptosis in a COX-2 independent manner (22). From this result, we should cautiously select the combination drug with COX-2 inhibitor.

Edelman *et al*. suggested the importance of exploring surrogate markers of efficacy and correlations with clinical outcome of COX-2 inhibitor using blood samples instead of tumor specimens, which can be subjected to immunohistochemistry because of the invasiveness of procedures for obtaining tumor specimens (5). This concept is definitely important regarding patients' quality of life. The blood samples using various methods, however, are still in debate in terms of their concordance of the molecular profile with tumor samples. In addition, obtaining an optimal amount of tumor samples is indispensable for establishing the genetic and epigenetic landscapes of the patients for the future use of individual molecular-based drugs. Thus, one future plan of the clinical trial using COX-2 inhibitors would still be better to utilize the tumor specimen subjected to immunohistochemistry using various antibodies and next-generation sequencing, loading several genes regarding COX-2/PGs pathway.

In conclusion, in the field of COX-2 inhibitor, there is still a lot of room for further investigation. Edelman's paper made us realize the importance of seeking for molecular-oriented therapy using COX-2 inhibitor, and we should keep the enthusiasm in exploring biomarkers and how to manage and bring better treatment with COX-2 inhibitor for patients with NSCLC by gaining a better understanding the biology of COX-2 in NSCLC.

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Footnote

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Comment on: Edelman MJ, Tan MT, Fidler MJ, *et al*. Randomized, double-blind, placebo-controlled, multicenter phase II study of the efficacy and safety of apricoxib in combination with either docetaxel or pemetrexed in patients with biomarker-selected non-small-cell lung cancer. J Clin Oncol 2015;33:189-94.

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