Cyclooxygenase-2 (COX-2) As a Predictive Marker for the Use of COX-2 Inhibitors in Advanced Non–Small-Cell Lung Cancer

TO THE EDITOR: Groen et al¹ recently reported the results of Nederlandse Vereniging voor Artsen Longziekten en Tuberculose (NVALT) –4, a prospective trial of celecoxib in addition to cisplatin and docetaxel in advanced non–small-cell lung cancer. Similar to previous results in unselected populations, no advantage was found for the addition of the cyclooxygenase-2 (COX-2) inhibitor. Retrospectively, the authors evaluated COX-2 expression and did not find a relationship between expression and outcome, a result that differs from that of the prospectively defined evaluation of COX-2 expression in the Cancer and Leukemia Group B (CALGB) trial 30203.² Groen et al imply that this may have been a result of the prevalence of adenocarcinoma as well as differences in performance status that were not accounted for in CALGB 30203. In fact, the proportion of patients with adenocarcinoma/squamous cell carcinoma in the two studies were virtually identical (49%/16% in NVALT-4 and 46%/20% in CALGB 30203). Age, sex, and performance status were included in the reported multivariate analysis that assessed the significance of COX-2 expression.

There are important differences between these trials that may explain the discrepancies. First, different chemotherapy regimens were used. NVALT-4 used cisplatin/docetaxel, whereas CALGB 30203 used carboplatin/gemcitabine. In vitro and clinical evidence demonstrates that antitubulin agents (eg, taxanes) induce COX-2 expression.^{3,4} It is possible that the continuing induction of COX-2 by docetaxel abrogated the beneficial effects of celecoxib. Therefore, the core regimen that is used may alter the potential benefit of COX-2 inhibition.

In support of the findings of CALGB 30203, retrospective evaluations of several phase II trials in lung, breast, and renal cancer have found that celecoxib in addition to other antineoplastic therapy results in improved outcomes in patients with elevated COX-2 expression.⁵⁻⁷

More recently, preliminary results of a randomized phase II trial that combined apricoxib (a COX-2 inhibitor that is similar to celecoxib) and erlotinib in patients with recurrent non–small-cell lung cancer who were selected on the basis of urinary prostaglandin E₂ metabolite suppression after 5 days of therapy with apricoxib demonstrated markedly improved progression-free survival in a prospectively defined cohort of patients age 65 years or younger.⁸

The NVALT-4 investigators¹ hypothesize that the dose of celecoxib (400 mg twice per day) may be insufficient to adequately suppress COX-2 on the basis of the findings by Reckamp et al⁹ of a greater degree of suppression of urinary prostaglandin E₂ metabolite (approximately 85% with doses > 600 mg twice per day v 65% with 400 mg twice per day) with higher doses of celecoxib. The authors¹ state that the dose of 400 mg twice per day may be inadequate to overcome higher degrees of COX-2 expression. However, our analysis of the COX-2 expression data from CALGB 30203 indicates that the dose of 400 mg twice per day is adequate and that, in fact, benefit was greatest in those with higher degrees of COX-2 expression (Table 1).

Data from more than 30 years of research in lung and other malignancies indicate that COX-2 expression is involved in the initiation, promotion, and perpetuation of malignancy and is associated with inferior outcome. We agree with the NVALT-4 investigators¹ that the results of strategies that inhibit COX-2 have been disappointing. However, given the substantial data that were generated in our multicenter cooperative group study and by others, we believe that the only way to conclusively answer this question is through a prospective, randomized trial that selects patients for therapy on the basis of COX-2 expression. Such a trial (CALGB 30801) is currently in progress.

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Table 1. COX-2 As a Predictive Factor: Comparison of Patients Who Did Not (n = 29; arm A) and Did (n = 54; arms B/C) Receive Celecoxib

End Point	Cut Point of COX-2 Index	n for Arm A v n for Arms B/C	HR	95% CI	P	Did Not Receive Celecoxib (arm A)		Did Receive Celecoxib (arms B/C)	
						Survival (months)	95% CI	Survival (months)	95% CI
OS	< 1	12 v 18	1.843	0.757 to 4.485	.178	13.3	7.3 to NR	8.1	4.9 to 14.9
OS	≥ 4	11 v 21	0.420	0.184 to 0.9555	.039	3.8	0.9 to 10.5	10.6	8.3 to 17.6
OS	≥ 9	6 v 14	0.194	0.060 to 0.629	.006	4.0	3.4 to 6.5	11.3	8.0 to NR
FFS	< 1	12 v 18	0.866	0.408 to 1.835	.707	3.9	3.1 to 5.2	3.9	2.8 to 4.6
FFS	≥ 4	11 v 21	0.312	0.135 to 0.718	.006	3.4	0.8 to 6.4	6.5	4.8 to 8.4
FFS	≥ 9	6 v 14	0.218	0.070 to 0.681	.009	3.8	3.3 to 4.2	6.5	5.5 to 10.5

Abbreviations: COX-2, cyclooxygenase-2; FFS, failure-free survival; HR, hazard ratio; NR, not reached; OS, overall survival.

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Reply to M.J. Edelman et al

We appreciate the critical discussion on cyclooxygenase-2 (COX-2) expression by Edelman et al.¹ Some comments can be made. We agree with Edelman et al that the differences in adenocarcinoma and squamous cell carcinoma between the Nederlandse Vereniging voor Artsen Longziekten en Tuberculose (NVALT) –4 study² and the Cancer and Leukemia Group B (CALGB) trial 30203³ are small. In CALGB 30203 (Table 1 of original article),³ 50% of patients had adenocarcinoma and 21% had squamous cell carcinoma, whereas in the NVALT-4 study (Table 1 of original article),² 48% of patients had adenocarcinoma and 18% had squamous cell carcinoma, respectively. It was not our intention to compare the two studies on the basis of these characteristics. The problem we encountered during our analysis was that both performance status as well as the presence of adenocarcinoma influence outcome. The association of high COX-2 expression with better performance status and the presence of adenocarcinoma, both characteristics associated with better survival, required adjustment for this reason. The prognostic information that COX-2 expression exhibited in the univariate analysis was reduced when adjusting for these characteristics. We note, however, that our COX-2 analysis cohort was not large, and results should be considered in this light.

In our study,² we used carboplatin and docetaxel for four cycles and celecoxib during induction and as maintenance until progression of disease. The only difference between the two studies^{2,3} with respect to chemotherapy was the use of docetaxel versus gemcitabine. We agree that the protein COX-2 expression is increased by taxanes. The increased COX-2 expression resulting from the use of taxanes would be beneficial during at least the

chemotherapy part of the study. This hypothesis can be tested by comparing tumor responses in both arms. The tumor response rate in the celecoxib arm was 38% compared with 30% in the placebo arm ($P = .08$). Although there is a numerical difference, we could not confirm the hypothesis of Edelman et al¹ in patients with advanced non-small-cell lung cancer.

Edelman et al¹ also raised the question of whether the celecoxib dose of 400 mg twice per day is adequate. In our study, we observed a trend of better survival in patients who had squamous cell carcinoma and were treated with celecoxib. Patients with squamous cell carcinoma generally demonstrate low COX-2 expression. These observations were the reason that we stated in our article² that the celecoxib dose may be inadequate to overcome higher COX-2 expression. This is in line with the observations of Reckamp et al.⁴

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