Patient selection for chemoprevention

COX-2 SAFETY

Elena Tsvetkova, MD, FRCPC, Medical Oncologist, Juravinski Cancer Centre, Hamilton

TRIAL SUMMARY: Celecoxib trial reexamined

Wang J, Cho NL, Zauber AG, et al. Expression of COX-2 and 15-PGDH in adenomas removed during pretreatment colonoscopy to predict chemopreventive efficacy of the selective COX-2 inhibitor, celecoxib. *J Clin Oncol* 35, 2017 (suppl 4S; abstract 524).

The Adenoma Prevention With Celecoxib (APC) trial in 2005 showed that patients at high risk for colorectal adenoma development experienced a 33% to 45% reduction in post-polypectomy adenoma detection when treated with the selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib. However, the study also found a small increased risk of cardiovascular toxicity among celecoxib users, preventing broad use of this agent for chemoprevention. Celecoxib inhibits expression of prostaglandin E2 (PGE2), an inflammatory mediator produced by fatty acid metabolism via cyclooxygenases, and degraded through the activity of 15-prostaglandin dehydrogenase (15-PGDH).

In this study, adenomas collected from APC trial participants prior to treatment were examined using immunohistochemistry, and categorized according to high or low expression of COX-2, and present or absent 15-PGDH. These measures were combined to estimate tumour PGE2 levels and separate cases into two groups: PGE2 low (COX-2 low/15-PGDH present); and PGE2 high (COX-2 high/15-PGDH present; COX-2 high/15-PGDH absent; or COX-2 low/15-PGDH absent). Mantel-Cox test was used to evaluate whether markers of PGE2 expression in these adenomas predicted benefit from celecoxib treatment for adenoma detection after polypectomy.

Results: Biomarker determinations were achieved for 71% of patients with available outcome data (n=1,295). Patients whose baseline adenomas demonstrated elevated COX-2 achieved the greatest overall reduction in adenoma risk with celecoxib treatment (risk reduction [RR] 0.37; p=0.0001). This risk reduction was less significant in the low COX-2 category (RR 0.64). Patients with low estimated tumour PGE2 did not benefit from celecoxib for adenoma prevention (RR 0.95; p=0.83). However, there was a 41% reduction in adenoma detection with celecoxib treatment for patients in the high PGE2 category (RR 0.59; p<0.0001). Immunohistochemistry to determine expression of target enzymes in premalignant adenomas provides significant prognostic and predictive information in patients treated with celecoxib for prevention of colorectal adenomas.

COMMENTARY: On many occasions, adenomas are precursors of CRC, so prevention of adenoma recurrence may play a significant role in preventing cancer development and associated morbidity and mortality. The 2005 APC trial demonstrated a 33% to 45% reduction rate in post-polypectomy adenoma detection when patients were treated with selective cyclooxygenase-2 inhibitor (COX-2) celecoxib.[6] However, it came at the expense of increased incidence of death from cardiovascular causes.[6,7] The present trial evaluated expression of COX-2 (high vs low) and 15-PGDH (present vs absent) and their role as predictors of celecoxib benefit in the prevention of adenoma recurrence.

The study demonstrated that celecoxib significantly reduced adenoma recurrence in both high-expression and low-expression COX-2 groups, with a trend toward better results in the high COX-2 group (with a RR of 0.37 versus 0.64, respectively). This study significantly contributes to personalized medicine, providing valid biomarkers to guide treatment and balance the benefits of therapy against possible adverse events.

References:

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IN BRIEF

Already known

- The selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, reduces the risk of post-polypectomy adenoma detection in patients at high risk for colorectal adenoma.
- There is a small increased risk of cardiovascular toxicity among celecoxib users, preventing broad use in chemoprevention.

What this study showed

- A subgroup of high-risk patients with high expression of prostaglandin E2 (PGE2) was found to have significant (41%) risk reduction with celecoxib, whereas patients with low expression did not benefit.

Next steps

- Use this biomarker to guide chemoprevention and balance the benefits of therapy against possible adverse events.

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