EDITORIAL

Celecoxib for Stage III Colon Cancer

David J. Kerr, MD, DSc; Sarah Chamberlain, BMedSci, MBChB; Rachel S. Kerr, MBChB, PhD

Observational studies have linked aspirin and selective cyclooxygenase-2 (COX-2) inhibitors to prevention of colorectal adenomas and colorectal cancer, and reduction in recurrence following resection or improved survival for patients with advanced or metastatic disease.[1-3] There are plausible mechanistic hypotheses linking inhibition of prostaglandin synthesis, nuclear factor κB activation,[4] and the transcription factor RUNX1[5] to the anticancer effects of aspirin and celecoxib. In addition, there is evidence from a meta-analysis across multiple studies of the potential effects in terms of enhanced response rates when COX-2 inhibition was added to standard chemotherapy in advanced colorectal cancer and other solid cancers. However, this improvement did not translate to an improvement in 1-year survival.[6]

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In this issue of *JAMA*, Meyerhardt and colleagues[7] report findings from a randomized, 2 × 2 factorial clinical trial that compared the selective COX-2 inhibitor celecoxib vs placebo, administered for 3 years, as an addition to conventional adjuvant chemotherapy (for 3 or 6 months) following resection of stage III colon cancer. Only the results of the celecoxib randomization are presented. The results based on the duration of adjuvant chemotherapy have been reported previously.[8] In this clinical trial that involved 2526 patients, the addition of celecoxib for 3 years, compared with placebo, to standard adjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) did not significantly improve disease-free survival (76.3% vs 73.4% at 3 years; hazard ratio [HR] for disease recurrence or death, 0.89, 95% CI, 0.76-1.03; $P = .12$). The effect of celecoxib treatment on disease-free survival did not differ significantly according to assigned duration of adjuvant chemotherapy (P for interaction = .61). Five-year overall survival was 84.3% for celecoxib-treated patients vs 81.6% for placebo-treated patients (HR for death, 0.86; 95% CI, 0.72-1.04; $P = .13$). Celecoxib was associated with a significantly increased risk of hypertension and elevation of creatinine levels; however, grade 3 or greater adverse events were not significantly increased.

The authors acknowledge 3 limitations in the study: First, adherence with randomized treatment and the duration of exposure to celecoxib or placebo were less than planned, with only approximately 70% of patients receiving assigned treatment for more than 2.75 years. However, for such a long-term study, this adherence level may be acceptable. As shown in Figure 3a in their article, the curves of percentage of patients with an event appears to suggest a divergence in event rates, comparing celecoxib vs placebo in the first 1 to 2 years. Thereafter the lines appear parallel, suggesting that perhaps if there is a small beneficial effect, this occurs early and is maintained. Assuming the reported estimated difference in disease-free survival and overall survival rates reported (2.9%) could be repeated in a larger trial, with statistical certainty, it is possible this observation may translate to a clinically acceptable patient benefit.

Second, the authors highlight that the original statistical assumptions of the trial assumed more rapid enrollment and more events than were achieved. This is a common occurrence in contemporary randomized adjuvant therapy trials globally. Both groups (treatment and placebo) generally experience better outcomes than expected, perhaps because the data upon which the assumptions about future trial survival are based always rely upon past data. For most diseases, treatments and surgical techniques and improvements in pathological assessment evolve over time, and these advances in clinical care will affect estimates of the anticipated survival of future patients recruited. The oncology research community needs to adapt and increase recruitment into adjuvant trials to allow adequate power when event rates are inevitably lower than projected.

Third, the authors point out that only patients with stage III colon cancer who already were receiving adjuvant chemotherapy were recruited into the trial, but patients with stage II colon cancer were excluded, which may increase the risk of a false-negative outcome in earlier stage disease. Although the VICTOR (Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime) trial was terminated early due to the worldwide withdrawal of rofecoxib yet in 2.5 years had randomize 2434 patients with colorectal cancer (between 2002-2004) who had undergone potentially curative surgery and completion of adjuvant therapy for stage II and III colorectal cancer to receive the COX-2 inhibitor rofecoxib or placebo, there was no significant benefit of rofecoxib compared with placebo on overall survival or disease recurrence after 5 years of follow-up.[9] However, subgroup analysis suggested a signal of possible benefit with less advanced disease, with the HR for death of 0.78 for stage II cancers and an HR of 0.96 for stage III cancers. Although the difference between the subgroups was not statistically significant (possibly due to the low numbers) and the results need to be interpreted with caution, it is feasible that the earlier stage the tumor, the more biologically similar it is to precancerous polyps that seem more susceptible to anti-COX effects, as shown in the PreSap (Prevention of Colorectal Sporadic Adenomatous Polyps) trial.[10]

Meyerhardt et al also point out that the trial did not select patients for enrollment based on molecular pathology. However, the state of knowledge in terms of biomarker selection

for response was not yet sufficiently robust at the time the trial was designed.

What are the next steps in terms of molecular segregation of colorectal cancer and the future development of adjuvant treatment of colorectal cancer? Trials are ongoing using "old-fashioned" aspirin in the adjuvant setting and these will be reported over the next 5 to 10 years (for example, NCT02804815). Although largely nonselective in terms of recruitment at the molecular level by collecting tissue and germline DNA and performing retrospective well-powered molecular analyses, these investigations could not only help define whether aspirin does reduce risk of recurrence of colorectal cancer after surgery but could also help confirm or refute the retrospective findings from previous studies that suggested the *PIK3CA* mutation can define an aspirin-responder population.[11,12]

In addition, the most significant molecular segregation development in colorectal cancer over the last 5 years has been the finding of responsiveness to immunotherapy (programmed cell death [PD] and its ligand [PD-L1] blockade) in advanced colorectal cancers that are mismatch repair deficient.[13] Immunotherapy is now being tested in the adjuvant setting in this subpopulation, for example in the ATOMIC trial (Alliance A021502; NCT02912559), which is a randomized phase 3 study of standard chemotherapy (modified FOLFOX-6) alone or in combination with atezolizumab as adjuvant treatment for patients with stage III colon cancer with tumors that are mismatch repair deficient.

In summary, the trial by Meyerhardt et al reported in this issue of *JAMA* contributes important data on the use of COX-2 inhibitors for patients after resection of stage III colon cancer and demonstrates that when added to standard adjuvant chemotherapy, celecoxib did not improve overall survival. The authors planned retrospective analyses and the analyses performed using samples gleaned from the ongoing aspirin studies may be helpful to define and may refine any potential role of aspirin, other COX-2 inhibitors, and other potential novel agents in patients with colorectal cancer.

ARTICLE INFORMATION

Author Affiliations: Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom (D. J. Kerr); Oxford University Hospitals Trust, Oxford, United Kingdom (Chamberlain); Department of Oncology, University of Oxford, Oxford, United Kingdom (R. S. Kerr).

Corresponding Author: David J. Kerr, MD, DSc, JR Hospital, University of Oxford, Oxford ox3 7dq, United Kingdom (david.kerr@ndcls.ox.ac.uk).

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA*. 2009;302(6):649-658. doi:10.1001/jama.2009.1112

2. Chan AT, Arber N, Burn J, et al. Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer Prev Res (Phila)*. 2012;5(2):164-178. doi:10.1158/1940-6207.CAPR-11-0391

3. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010;376(9754):1741-1750. doi:10.1016/S0140-6736(10)61543-7

4. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med*. 2007;356(21):2131-2142. doi:10.1056/NEJMoa067208

5. Voora D, Rao AK, Jalagadugula GS, et al. Systems pharmacogenomics finds RUNX1 is an aspirin-responsive transcription factor linked to cardiovascular disease and colon cancer. *EBioMedicine*. 2016;11:157-164. doi:10.1016/j.ebiom.2016.08.021

6. Chen J, Shen P, Zhang X-C, Zhao MD, Zhang XG, Yang L. Efficacy and safety profile of celecoxib for treating advanced cancers: a meta-analysis of 11 randomized clinical trials. *Clin Ther*. 2014;36(8):1253-1263. doi:10.1016/j.clinthera.2014.06.015

7. Meyerhardt JA, Shi Q, Fuchs CS, et al. Effect of celecoxib vs placebo added to standard adjuvant therapy on disease-free survival among patients with stage III colon cancer. *JAMA*. Published April 6, 2120. doi:10.1001/jama.2021.2454

8. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378(13):1177-1188. doi:10.1056/NEJMoa1713709

9. Midgley RS, McConkey CC, Johnstone EC, et al. Phase III randomized trial assessing rofecoxib in the adjuvant setting of colorectal cancer: final results of the VICTOR trial. *J Clin Oncol*. 2010;28(30):4575-4580. doi:10.1200/JCO.2010.29.6244

10. Arber N, Eagle CJ, Spicak J, et al. PreSAP Trial Investigators. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med*. 2006;355(9):885-895. doi:10.1056/NEJMoa061652

11. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor *PIK3CA* mutation, and colorectal-cancer survival. *N Engl J Med*. 2012;367(17):1596-1606. doi:10.1056/NEJMoa1207756

12. Domingo E, Church DN, Sieber O, et al. Evaluation of *PIK3CA* mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. *J Clin Oncol*. 2013;31(34):4297-4305. doi:10.1200/JCO.2013.50.0322

13. Ganesh K, Stadler ZK, Cercek A, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. *Nat Rev Gastroenterol Hepatol*. 2019;16(6):361-375. doi:10.1038/s41575-019-0126-x