Perspective

Perspective on Sabichi et al., p. XXX

Boxing Bladder Cancer with COX-2–specific Inhibition

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Abstract

Preventing recurrence of non-muscle–invasive bladder cancer (NMIBC) is important for improving patient well-being and reducing the health economic burden of this disease. To date no oral agent has shown sufficient benefit to be adopted in clinical practice, where current strategies rely on topical (intravesical) administration of chemotherapy and immunotherapy. In this issue of the journal (beginning on page XXX), Sabichi and colleagues report the first phase II randomized controlled trial of the cyclooxygenase-2 (COX-2) inhibitor celecoxib in bladder cancer. The trial set out to measure an overly ambitious effect size but nevertheless showed encouraging signs of celecoxib activity. It lends support to COX-2 inhibition in NMIBC, which is being tested in several subsequent trials, and to the need for conclusive evidence.
The body of evidence pointing to the cyclooxygenase-2 (COX-2) pathway as playing an important role in the development of bladder neoplasia is compelling and supported by several epidemiological studies (1). Paralleling early development in colorectal cancer prevention, where the COX-2–specific inhibitor celecoxib [a nonsteroidal anti-inflammatory drug (NSAID)] is clinically effective, preclinical studies confirm that celecoxib can prevent neoplastic transformation of urothelium and reduce urothelial tumor burden in vivo as a single agent or in combination with the immunomodulator bacillus Calmette-Guérin (BCG; refs. 2, 3), which is standard adjuvant treatment for preventing recurrence of non-muscle–invasive bladder cancer (NMIBC). It is therefore not surprising that celecoxib is being tested in clinical trials in patients with NMIBC.

Sabichi et al. report the results of such a trial in this issue of the journal (4), but do the trial’s results paint a clear picture of the role of COX-2 inhibition in the setting of bladder cancer prevention? They conducted a phase IIb randomized placebo-controlled trial of celecoxib (200 mg bid) for a minimum of 12 months to prevent recurrence in 146 patients following transurethral resection of established NMIBC and adjuvant BCG. Time to recurrence was the primary endpoint, and the statistical design powered the trial to detect a 53% relative reduction in the risk of recurrence at 12 months. The trial was initiated in an era when an effect of celecoxib may have seemed assured, but designing a trial to detect a halving of the recurrence rate in a heavily pre-treated population was overly optimistic. It is not surprising that the primary endpoint did not reach statistical significance—the results are based on just 48 events and it is important to keep in mind that the estimated treatment effect was overly ambitious.

Nevertheless, the results do support the possibility of a clinically beneficial effect of celecoxib. The adjusted hazard ratio was 0.69 [95% confidence interval (CI), 0.37–1.29], and the absolute 12-month recurrence-free rates were 88% (95% CI, 81%–96%) in the celecoxib group and 78% (95% CI, 69%–89%) in the placebo group (log-rank test: \( P = 0.17 \)). The study did not detect a difference in the number of adverse cardiovascular (CV) events between the celecoxib and
placebo arms, although based on the known CV event rate of celecoxib at the trials’ dose and duration, a measurable effect would not have been expected (5).

Certainly the trends in this study suggesting that celecoxib may well be active in patients with NMIBC will be interpreted with cautious optimism by some, scepticism by others. Fortunately for the ultimate interpretation of these results, the ongoing phase III randomized controlled Bladder COX Inhibition Trial (BOXIT; ISRCTN 84681538; CR UK/07/004) of the same daily dose of celecoxib (albeit 400 mg once a day in BOXIT and 200 mg bid in Sabichi et al.) versus placebo for 24 months is being conducted in a similar patient population (intermediate- and high-risk NMIBC). Supported by the United Kingdom National Cancer Research Institute, BOXIT will complete accrual of over 400 patients in early 2012.

The known risk-benefit profile for COX-2 inhibition strategies has changed since the present and BOXIT trials were conceived; indeed, the trial by Sabichi et al. (4) was halted for a period following the discovery that adverse cardiac events were linked to COX-2 inhibitors in randomized controlled trials. The interruption does not seem to have affected the results, and a weighing up of the risk versus benefit for celecoxib in the bladder cancer setting suggests that patients with established NMIBC at a high risk of recurrence potentially will be the most appropriate group for celecoxib treatment. An exploratory analysis of Sabichi et al. suggests that the treatment effect was larger in the higher-risk subgroup of patients with multiple recurrences. Although the trial was not powered to look at this effect, the finding is interesting nonetheless. Currently these higher-risk patients have limited treatment options, and radical cystectomy, which is associated with considerable morbidity, is a standard of care following BCG failure. No oral or intravesical agent heretofore has produced a durable recurrence-free interval that would make it a candidate for standard of care in this group of patients.

What level of benefit will persuade patients and physicians to accept celecoxib for preventing recurrence of NMIBC? A study of celecoxib or aspirin for cancer prevention in the setting of Barrett’s esophagus found that patient acceptance of both agents was high, although
a preference for aspirin was clear (6). A number of clinical trials testing celecoxib in patients with established cancer have not reported issues relating to acceptance. The field awaits results of a large ongoing CV-outcome trial in arthritis patients comparing outcomes among celecoxib, naproxen, and ibuprofen (7) and results of the Coxib and traditional NSAID Trialists’ (CNT) Collaboration meta-analysis of data on serious vascular complications associated with coxibs (8), which will inform the risk-benefit discussion; other important data already indicate that celecoxib does not increase CV risk in individuals with a low baseline CV risk (5) or with a low level of C-reactive protein (CRP; ref. 9). The presumption is that the use of COX-2 inhibitors in high-risk cancer-prevention settings seems reasonable, as is born out by successful recruitment to the trial of Sabichi et al. in NMIBC. Whether this presumption would hold up in a trial powered to detect a smaller effect size than that assumed by Sabichi et al. is not clear.

BOXIT is powered to detect a 15% absolute reduction in three-year recurrence rates, which translates to a hazard ratio of 0.62 (versus placebo); this effect-size estimate is not inconsistent with the encouraging reduction reported by Sabichi et al. The similarities across the two trials in terms of celecoxib dose and patients’ risk profile would support a future meta-analysis of their combined results.

In conclusion, the present results of Sabichi et al. fan interest in continued primary research to advance our understanding of the roles of COX-2 and COX-2 inhibitors in bladder tumorigenesis. Broader efforts to dissect the interaction between tumor cells, the prostaglandin-rich environment, and the inflammatory process continue to focus on the role of COX-2 as an important mediator of neoplastic transformation and cancer progression. There is also continued potential for cross-fertilization between tumor types and between studies to understand COX-2 in the context of genetic susceptibility to cancer development and to explore pharmacogenomic factors with the potential for guiding selection of patients who may benefit most from COX-2 inhibitors. The research community can optimistically view the present results
of the phase II trial of Sabichi et al. as a positive contribution to a work in progress. The capstone of this work in NMIBC, results of the phase III BOXIT, are expected in 2014.
Potential Conflicts of Interest

John Kelly is the Chief Investigator and Emma Hall is the senior statistician of BOXIT.

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