

## Platinum Priority – Editorial

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# Can We Prevent Bladder Cancer Recurrences?

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Non-muscle-invasive bladder cancer (NMIBC), oft noted to be among the most expensive cancers on a per capita basis, is burdened by frequent recurrences and rarer occurrences of disease progression. Given the length of time patients spend with bladder cancer, this disease lends itself to consideration of chemoprevention strategies. In this issue of *European Urology*, Kelly and colleagues [1] present the results of BOXIT, a phase 3 randomized controlled trial in which they compared daily preventive celecoxib for secondary chemoprevention with placebo among patients with initial or recurrent intermediate- or high-risk NMIBC. Among all patients, time to recurrence did not differ between the treatment groups. Among a subgroup of patients with stage T1 high-grade cancers, there was benefit of celecoxib in delaying recurrences, although this subset analysis was underpowered and not a preplanned subgroup. However, any potential value is counterbalanced by the much higher rate of adverse cardiovascular events in the celecoxib arm (5.2% vs 1.7%). This contrasts with a recent trial among rheumatologic patients that found no increase in the risk of cardiovascular events among patients taking celecoxib versus naproxen or ibuprofen; there was no placebo arm [2].

BOXIT exemplifies an important new direction in scientific presentation: the importance of the negative result. We cannot correct mistaken clinical directions without acknowledgment of what does not work. Despite compelling preclinical and observational data, randomized trials refute causality. Other chemoprevention strategies that failed when confronted with a randomized trial include vitamin B6, retinoids, difluoromethylornithine, megadose vitamins, and selenium [3]. Until data demonstrate a therapeutic option for bladder cancer chemoprevention, clinicians should continue to educate patients on the

benefits of a healthy lifestyle in generic cancer prevention, including a diet rich in fruits and vegetables, exercise, and weight loss for overweight and obese patients.

Adjuncts are available for bladder cancer management that may mitigate the substantial risk of recurrence. Even among patients whose cancer does not progress, recurrence leads to patient-centered detriments, including loss of income, a decrease in urinary quality of life from resections and intravesical therapies, and anxiety related to a patient's cancer outcomes. Beyond pharmacologic prevention, what else can be done? Medical care is often confounded by the problem of doing too much. Yet in bladder cancer it seems like we actually do too little. Assessments of US data consistently demonstrate that few patients with high-risk NMIBC receive recommended intravesical therapy and adequate surveillance assessments [4,5]. Ensuring that patients have access to induction and maintenance treatment with intravesical bacillus Calmette-Guérin (BCG) may reduce the burden of recurrences at a population level.

What else can urologists do? Among active smokers at the time of bladder cancer diagnosis, we know that the urologist has an opportunity to harness a “teachable moment” and impact a patient's smoking behavior [6]. In retrospective studies, smoking cessation is associated with a decrease in the risk of recurrence and in the incidence of disease progression among patients with NMIBC [7]. Yet despite this potential role in a patient's reclamation of health and reduction in the risk of future bladder cancer recurrence, many urologists feel uncomfortable promoting smoking cessation [8]. Although fatalism may play a role, self-acknowledged lack of comfort in smoking cessation counseling is a predominant factor [8]. Given the availability of publicly sponsored smoking cessation resources, the feasibility of offering pharmacologic therapy to aid in

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smoking cessation, and the reality that acknowledging the relationship between a patient's ongoing smoking and their cancer is often associated with a quit attempt [9], smoking cessation needs to be in the armamentarium of any practicing urologic oncologist.

Celecoxib is not going to be routinely used as a secondary chemopreventive agent in the care of newly diagnosed or recurrent NMIBC. That knowledge has an impact on clinical bladder cancer practice and patient counseling. These findings mandate a renewed focus on other care pathways such as compliance with induction and maintenance BCG and attention to behavioral interventions such as smoking cessation.

**Conflicts of interest:** The authors have nothing to disclose.

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