Chemoprevention in bladder cancer: What's new?

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Abstract

Bladder cancer is the sixth most common tumour in Canada and ranks eighth in terms of cancer mortality. Up to now, management of this condition relied mostly on surgical and intravesical treatments once the disease is established. Chemoprevention is an attractive option to prevent the disease in high-risk populations and may well reduce the costs related to its treatment. This review examines the available data on chemoprevention strategies in bladder cancer, with special emphasis on randomized controlled trials when available.

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Introduction

Bladder cancer (BC) is one of the most expensive cancers to treat in North America due to its recurrent nature necessitating investigative follow-up and intravesical treatments, and due to comorbidities related to major surgery in cases of invasive cancer. In Canada, BC represents the sixth most common tumour type and ranks 8th with respect to cancer mortality.[1] Of the 3 main histological variants of BC (Table 1), transitional cell carcinoma is the most prevalent in North America,[2] and thus constitutes the object of this review.

For a variety of reasons, BC is a disorder very well suited to chemoprevention. First, its natural history is characterized by frequent recurrences, which need to be minimized. Second, in addition to the role of genetic susceptibility, the pathogenesis of BC also correlates with environmental factors such as cigarette smoking, implying sustained contact of urinary carcinogens with the urothelium. The rationale behind chemoprevention lies, therefore, in reducing or preventing the intimate contact of these chemicals with bladder mucosa. Additionally, chemopreventive compounds administered systemically and excreted in urine have the favourable pharmacokinetic property of remaining in close prolonged contact with bladder epithelium. Finally, diagnostic methods in BC allow easy bladder access and tissue sampling for evaluation of the efficacy of prevention strategies.

Three types of prevention have been defined: primary prevention, which focuses on avoiding development of cancer in healthy subjects; secondary prevention, which targets premalignant lesions with the intent of avoiding their progression to cancer; and tertiary prevention, which focuses on preventing cancer progression in patients diagnosed with and treated for the disease. Primary and tertiary prevention strategies apply well to BC. However, in the case of primary prevention, because it pertains to a nonafflicted population, this strategy implies that the trade-off between the risk/inconvenience of intervention and the anticipated benefit is substantial. It also implies that a population at risk, in which intervention is warranted, can be identified. These restrictions make primary intervention, albeit attractive conceptually, somewhat difficult to implement in practice. Tertiary intervention is already widely practiced in BC in the form of intravesical treatment, but other alternatives with less toxicity have yet to be explored. This review reports on recent progress made in the field of BC chemoprevention, with emphasis on interventional strategies.

Dietary modifications

Fluid intake

Increased hydration has been touted as a potentially effective strategy for BC prevention based on the idea that dilution of urinary carcinogens and increased urinary flow result in decreased contact of carcinogens with the urothelium.[3] This concept has been clinically validated in the Health Professionals Follow-up Study.[4] Evaluating mailed questionnaires of 47 909 men, the results of this study suggested that total daily fluid intake was inversely associated with risk of BC, with a relative risk of 0.51 (0.32-0.80, 95% Confidence Interval [CI]) in those who consumed the highest levels of fluid. Daily water consumption seemed to provide the best protection when compared to other fluids. These results were contradicted by another large, multicentre, case-control study by Geoffroy-Perez and colleagues that included both men and women.[5] Their conclusion suggested an absence of association between fluid consumption and BC risk. Furthermore, they reported an increased incidence of cancer related to coffee consumption, albeit with a weak association,[5] and a finding already reported in a study by

Table 1. Histologic variants of bladder cancer and their frequencies according to the SEER database

Histology	Frequency
Transitional cell carcinoma	93.6%
Squamous cell carcinoma	2.1%
Adenocarcinoma	1.4%
Unspecified	2.2%

Adapted from Lynch et al.[2]; SEER: Surveillance, Epidemiology and End Results.

Sala and colleagues.[6] This controversy precludes definitive recommendations with regards to fluid intake in BC.

Lipids and caloric intake

In a multicentre study conducted in Spain, Riboli and colleagues first established an association between fat consumption and BC, showing more than a 2-fold increase in cancer incidence.[7] Population-based, case-control data using the Surveillance, Epidemiology and End Results (SEER) database have provided further evidence that fat-rich diets are associated with an increase in BC occurrence (OR 2.24 for the highest quartile, 95% CI 1.25-4.03, $p = 0.006$).[8] It also seems that this association is dose-dependent, according to at least one Swedish study.[9] Finally, in a meta-analysis of 36 studies assessing 6 dietary variables in relation to BC, Steinmaus and colleagues found the same positive association with fat intake (Relative ratio [RR] 1.37, 95% CI 1.16-1.62) but not with meat intake (RR 1.08, 95% CI 0.82-1.42).[10] In the Health Professionals Follow-up Study, there was no observed association between total caloric intake and BC risk over a 12-year follow-up period.[11] Unfortunately, aside from the general flaws related to these epidemiological studies, such as recall bias and lack of prospective data, one potential confounding variable in lipid intake studies is the concomitant increased total caloric intake in populations with high-fat diets. Despite these caveats, it would probably be safe to recommend a low-fat diet as a chemopreventive measure for BC given an overall "collateral" benefit.

Green tea

Green tea contains polyphenols, and these compounds have been shown to possess potent antioxidant activity.[12] They may also act by inhibiting the action of ornithine decarboxylase, an enzyme that promotes tumour proliferation through nucleic acid regulation.[13] There is preclinical evidence to suggest green tea as a potent chemopreventive agent against BC.[14,15] The incidence of BC in Asian populations with elevated tea consumption is lower than that in North America, providing a circumstantial argument in favour of the beverage.[16] In addition, a weak inverse relationship between green tea intake and BC has also been reported in at least 1 epidemiological study.[17] The effect of green tea in BC remains controversial, however, and NCI-sponsored phase 2 and 3 clinical trials are underway in order to establish its best use in urothelial tumours.[18]

Soy

Due to their high isoflavone content, soy products exert potent apoptotic and antiangiogenic action.[19] The role of soy products in BC, however, has not yet been established. In fact, an epidemiological study by Sun and colleagues in a Singapore-based population actually revealed an increased risk of BC in subjects with high consumption of soy food, with the highest quartile intake associated with a 2.3-fold increase in BC risk (95% CI 1.1-5.1).[20] This risk was independent of smoking history. Since soy food is probably protective in prostate cancer, according to available data, patients consuming it for this indication should be counselled on its potential association with increased risk for bladder tumours.

Vitamins and supplements

Vitamin A and its analogues

Vitamin A exists in a natural form and synthetic formulations, also known as retinoids. Aside from preclinical studies demonstrating activity in BC, epidemiological data in humans seem inconsistent. Many reports have suggested benefit from retinoid supplementation, including a SEER database, case-control study where 1592 BC subjects were compared to an equal number of matched neighbourhood controls. It was found that carotenoids were mostly beneficial in current or previous smokers.[21] However, using urine cytoflowmetry as a biomarker, the authors of a randomized trial using fenretinide were unable to detect any difference between the treatment and placebo arms in a sample of 99 patients.[22] In another prospective, randomized, double-blind study, Studer and colleagues evaluated the effect of etretinate in 90 patients having undergone transurethral bladder tumour resection for stage Ta and T1 cancers. Although the observed time to first recurrence in this study was similar in treatment and placebo groups, time to second recurrence was significantly longer in the etretinate arm (20.3 vs. 12.7 months, $p < 0.006$).[23] The authors concluded that this may imply that etretinate may not act on established microscopic tumours but could prevent the occurrence of new lesions.

High vitamin A intake is additionally associated with a toxicity syndrome including respiratory insufficiency, low blood pressure and fever. Toxicity with little measurable

benefit was notably a reason for prematurely closing the National Bladder Cancer Collaborative Group study, the aim of which was to evaluate 13-cis-retinoic acid in subjects treated for Ta and T1 bladder tumours with a high risk of recurrence.[24] New synthetic formulations have, however, rendered toxicity problems insignificant, with very few grade 3 and 4 episodes reported.

In light of the available data, it is probably acceptable to recommend vitamin A supplementation, but caution should be exercised in supplementing above the recommended daily allowance.

Vitamin B6 (pyridoxine)

In a Veterans Administration clinical trial using a 3-arm design, Byar and colleagues randomized 121 patients to receive placebo, pyridoxine or intravesical thiotepa. When patients followed for less than 10 months were excluded, pyridoxine provided better activity than placebo and was as efficacious as thiotepa in reducing recurrence ($p = 0.03$).[25] These initial positive results were not reproduced by an EORTC, randomized, phase 3 trial of 291 patients, which showed no difference between vitamin B6 and placebo in terms of time to first recurrence or recurrence rate.[26] Vitamin B6 cannot therefore be recommended as a stand-alone chemoprevention strategy in BC.

Vitamin C

Ascorbic acid, also known as vitamin C, is another compound with known potent antioxidant properties. Its activity in preventing BC has been shown in human epidemiological studies.[11,27] The beneficial effect seems further related to the amount of consumption, with higher intake being associated with even lower risk.[28] Unfortunately, these results have not been consistently reproduced, with some epidemiological data failing to demonstrate benefit from vitamin C in large cohorts.[29] Nonetheless, the available data suggest a beneficial role for vitamin C supplementation that deserves further investigation.

Vitamin E

Yet another antioxidant molecule, vitamin E also exhibits apoptotic properties, and is known to reduce N-nitroso compounds, which are carcinogenic in BC. Multiple studies have shown an inverse association between vitamin E intake and BC incidence.[7,8,11] A meta-analysis by Miller and colleagues has, however, shown a potential increase in all-cause mortality related to vitamin E supplementation.[30] Such findings make recommendations on chemoprevention with this molecule not warranted for the time being.

Vitamin megadoses

Instead of studying each vitamin individually, Lamm and colleagues combined multiple vitamins (A, B6, C, E and zinc) with documented activity against BC in a randomized study of 65 patients receiving intravesical bacillus Calmette-Guérin (BCG).[31] This approach conceptually provides the benefit of synergistic action with the possibility of reduced toxicity. Yet megadoses were used in a 2 x 2 design, where patients were randomized to receive intradermal BCG or not, and also randomized to receive megadose vitamins versus recommended daily allowance. Intradermal BCG did not affect outcome. However, megadose vitamins were associated with a 50% risk reduction of overall recurrence at 4 years. As the only study assessing megadose vitamins, this small trial does not allow generalized recommendation without further assessment of such a regimen in BC.

Selenium

The role of selenium in BC is controversial. Although some studies suggest reduced levels of this oligoelement in BC patients,[32] other studies fail to establish this correlation.[33] A Belgium-based phase 3, randomized trial evaluating selenium in the prevention of cancer recurrence in patients with non-muscle-invasive BC has been underway since June 2008. Enrolment is expected to reach 900 subjects. It is hoped that results of this trial will help shed some light on the role of selenium as a chemopreventive agent in BC.[18]

COX inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase (COX) enzyme, which is responsible for the breakdown of arachidonic acid into leukotrienes and prostaglandins. It has been shown that prostaglandin-2 can drive cell proliferation, and has angiogenetic as well as anti-apoptotic properties. In vitro evidence points to overexpression of the isoform COX2 in bladder transitional cell carcinoma.[34,35] It is therefore rational to use COX inhibitors, and specifically the COX2 isoform, as possible chemopreventive agents in this disease. In a population-based, case-control study, Castelao and colleagues evaluated the use of NSAIDs with respect to BC incidence and found a 19% reduction in BC risk in patients taking NSAIDs other than phenacetine and pyrazolone derivatives.[36] Although there is preliminary evidence regarding the effects of specific COX2 inhibitors, results from clinical trials are still pending.[37]

Difluoromethylornithine

Ornithine decarboxylase (ODC) is an enzyme that promotes polyamine production, which in turn promotes tumour growth.

Although preclinical studies showed promise for difluoromethylornithine (DFMO) (a competitive inhibitor of ODC) in the setting of BC, this has not been translated into positive results in human subjects. In a randomized, phase 3 study conducted by Messing and colleagues, supplementation with 1g of DFMO daily did not reduce the recurrence rate of completely resected low-grade bladder tumours when compared to placebo.[38] This trial had a high dropout rate. The current clinical evidence thus does not support the use of DFMO in BC chemoprevention, and further studies are required.

Conclusion

Bladder cancer is a disorder very well suited to chemoprevention and although efforts to establish active agents have come a long way, research is still in the embryonic phase. Clinical data seem to suggest activity for at least some agents that merit further investigation—these include vitamin A, vitamin C, megadose vitamins and COX2 inhibitors. Selenium is certainly a promising compound and results of clinical trials are awaited with anticipation. The development of validated biomarkers that can be used as surrogate study endpoints would ultimately render chemopreventive agent validation more readily feasible.

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