A survey of physician perception and practices regarding pharmacological thromboprophylaxis during chemotherapy for bladder cancer

Andrew Amenyogbe[1], Francis Lemire[1], David Yachnin[2], Marc Carrier[2,3], Kristen McAlpine[4], Rodney H. Breau[1,2], Dominick Bossé[2,5], Tzu-Fei Wang[2,3], Christopher Morash[1], Ilias Cagiannos[1], Luke T. Lavallée[1,2]

[1]Division of Urology, Department of Surgery, University of Ottawa, Ottawa, ON, Canada; [2]The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [4]Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada; [5]Division of Medical Oncology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

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Abstract

Introduction: Patients with advanced bladder cancer receiving chemotherapy have a high risk of venous thromboembolism (VTE); however, we hypothesized these patients were not routinely offered thromboprophylaxis. The objective of this study was to characterize practice patterns and perceptions of Canadian urologic and medical oncologists, and to identify research needs regarding thromboprophylaxis for patients with bladder cancer.

Methods: An online survey was distributed to Canadian urologic and medical oncologists who manage advanced bladder cancer. The survey explored physician opinions regarding VTE rates, risk stratification scores, thromboprophylaxis use in different treatment settings, and interest in clinical trials.

Results: Seventy physicians were invited and 36 (51%) completed the survey, including 20 (56%) urologic oncologists and 16 (44%) medical oncologists. Most respondents (35; 97%) believed that exposure to platinum chemotherapy increases VTE risk. For patients receiving neoadjuvant chemotherapy, 34 (94%) respondents estimated the risk of VTE to be 10% or higher, yet 25 (69%) indicated they do not routinely recommend thromboprophylaxis. Physicians frequently (10; 40%) defer the decision to another physician, while eight (32%) believe there is not enough evidence to guide best management. Similar responses were obtained for metastatic patients. Almost all (94%) respondents were interested in participating in a thromboprophylaxis trial for patients with bladder cancer.

Conclusions: Patients with bladder cancer receiving chemotherapy in Canada are not routinely offered thromboprophylaxis. We found strong interest among Canadian oncologists to participate in clinical trials examining this topic.

KEY MESSAGES

- Physicians in Canada believe that patients with advanced bladder cancer have a high risk of venous thromboembolism.
- There is evidence to support thromboprophylaxis in patients receiving chemotherapy, but data may not be generalizable to patients with bladder cancer, as few of them were included in prior trials.
- Physicians in Canada do not routinely offer thromboprophylaxis to patients with bladder cancer receiving chemotherapy.
- Medical and urological oncologists in Canada have a strong interest to participate in clinical trials examining thromboprophylaxis in bladder cancer patients.

Introduction

Over 12 000 patients are diagnosed with bladder cancer in Canada each year.[1] Patients with cancer are at nine times higher risk of venous thromboembolism (VTE) than the general population (2.3% compared to 0.4%, respectively) and VTEs are the leading cause of non-cancer-related death in patients who receive cancer surgery.[2,3] A population-based study reported that for patients with cancer, exposure to chemotherapy significantly increases the risk of VTE over a 12-month period compared to no exposure to chemotherapy (hazard ratio [HR] 3.4).[3]

Several stratification tools exist to estimate the risk of VTE for patients with cancer receiving chemotherapy, the most common being the Khorana score.[4] Patients with bladder cancer are at higher risk of VTE than other cancer patients.[4-6]

This may be due to the underlying biology of the cancer, the location of the bladder in the pelvis, which may impact vascular function (such as compression of iliac veins), and treatment types (surgical or systemic). In addition, platinum chemotherapies, which are commonly used to treat bladder cancer, are associated with a higher risk of VTE than other types of chemotherapies.[7,8]

Randomized trials have demonstrated that thromboprophylaxis with a direct oral anticoagulant (DOAC) reduces the risk of VTE by approximately 60% in ambulatory cancer patients with intermediate to high risk of VTE (defined as Khorana score ≥2) receiving chemotherapy.[9,10] The generalizability of these results to the bladder cancer population is unknown because there were only five patients with bladder cancer in the AVERT trial and 32 with genitourinary (GU) (bladder, testis, ureter, kidney) cancers in the CASSINI trial.[9,10]

Current guidelines from the American Society of Hematology (ASH) stratify cancer patients starting chemotherapy into risk categories using the Khorana score and recommend thromboprophylaxis for high-risk patients. For intermediate-risk patients, the ASH provides a conditional recommendation for thromboprophylaxis or no thromboprophylaxis, due to the lack of certainty surrounding the benefit-risk ratio.[11] Given the lack of data directly addressing thromboprophylaxis during chemotherapy for patients with bladder cancer, it is likely that practice patterns across Canada are variable and could be improved with additional research. This variability has been reported in a previous survey among physicians of one Canadian academic center.[12]

We hypothesized that patients with bladder cancer receiving chemotherapy in Canada were not routinely offered thromboprophylaxis. The objective of this study was to characterize thromboprophylaxis practice patterns of Canadian urologic oncologists and medical oncologists, to identify current research gaps in this area, and to assess physician interest regarding clinical trials studying the role of thromboprophylaxis during chemotherapy for patients with bladder cancer.

Methods

A cross-sectional, observational study was performed using an online survey. Institutional ethics review board approval was obtained (REB Protocol 20210413-01H). A pilot questionnaire was developed and tested among three uro-oncologists and one medical oncologist in June 2021. Survey questions were revised for clarity and content using feedback received in the pilot survey. Questions were formatted as multiple choice or short answer. Survey responses were anonymous; however, respondents had the opportunity to provide their contact information if they were interested in participating in future related clinical trials.

An electronic survey was generated on LimeSurvey® and distributed via email. All questions and answers were in English. The survey was distributed to urologic oncologists and medical oncologists in Canada who manage advanced bladder cancer. Eligible participants were identified by study investigators based on prior participation in national meetings or membership in subspeciality associations related to management of advanced bladder cancer. Two emails (one initial and one reminder) containing a secure link to the questionnaire were sent between July 30, 2021 and September 19, 2021.

Survey questions were designed to assess physicians' perceptions and practice patterns related to thromboprophylaxis in patients with bladder cancer undergoing chemotherapy. The first question of the survey confirmed that the respondent managed patients with advanced bladder cancer. The survey was stopped for respondents who indicated they did not manage advanced bladder cancer.

The survey was then divided into four sections of questions. In the first section, participants were questioned regarding their perception of VTE risk for patients with bladder cancer receiving chemotherapy, as well as their familiarity with VTE risk scores, such as the Khorana score and CATScore.[4,13] The Khorana score assigns points based on cancer type, body mass index, and laboratory parameters (elevated platelets, low hemoglobin, and high leukocyte count), with higher scores associated with higher risk of VTE. The CATscore assigns risk using cancer site and D-Dimer level prior to chemotherapy.

The second section explored the respondents' current practices and perceived barriers or concerns with thromboprophylaxis in different clinical settings, including neoadjuvant chemotherapy for patients with localized disease and chemotherapy for patients with metastatic disease. For example, physicians were asked if they routinely offer thromboprophylaxis and if so, how they select patients. Reasons for not offering thromboprophylaxis were also explored.

The third section evaluated physicians' familiarity, knowledge, and opinions about existing evidence related to thromboprophylaxis in patients with cancer.

In the final section, the survey explored opinions regarding future research needs (knowledge gaps) that exist related to thromboprophylaxis for patients with bladder cancer and gauged interest in participating in clinical trials on this topic. Basic information of respondents, including subspeciality (medical or urologic oncology), province of practice, and years since finishing training, was collected to determine if these characteristics were associated with responses. The full survey is available as an Appendix (at *cuaj.ca*).

Descriptive analyses of survey responses were reported for all respondents and stratified by subspeciality (urologic oncology and medical oncology) because it was anticipated that practice patterns and perceptions vary between specialities. Respondents who terminated the survey early after initiation and completed <10% of the questions were excluded.

Results

Respondent demographics

Seventy physicians were emailed the online survey, including 32 urologic oncologists and 38 GU medical oncologists. There were 38 physicians who initiated the survey; however, two responders were excluded because they terminated the survey prematurely (<10% completed), leaving 36 (51%) with complete responses. Twenty urologic oncologists (56%) and 16 medical oncologists (44%) provided complete responses. All 36 respondents included in analyses reported managing patients with invasive bladder cancer who may receive chemotherapy. Respondents had varying experience in practice, with five (14%), 11 (31%), and 11 (31%) reporting being in practice for 5–10 years, 11–20 years, and more than 20 years, respectively. Nine (25%) did not indicate their years of practice. Respondents included physicians practicing in seven Canadian provinces, with half working in Ontario (Table 1).

Perception of VTE risk during chemotherapy

Thirty-five respondents (97%) believed that exposure to platinum-based chemotherapy increases the risk of VTE, including all medical oncologists and all but one urologist. For patients receiving neoadjuvant chemotherapy for bladder cancer, two (6%) physicians estimated the risk of developing VTE to be less than 5%, while 19 (53%), seven (19%), five (14%), and three (8%) estimated the risk to be 10%, 15%, 20%, and ≥20%, respectively (Figure 1). Twenty-three (64%) respondents were familiar with at least one validated score to stratify VTE risk (Khorana score or CATScore) and Khorana score was the most known. Thirteen (36%) physicians were not familiar with either score, 11 (85%) of whom were urologists.

Table 1. Demographic data of respondents

	n (%)
Year in practice	
<5	0 (0)
5–10	5 (14)
11–20	11 (31)
>20	11 (31)
Not specified	9 (25)
Medical discipline	
Urologic oncology	20 (56)
Medical oncology	16 (44)
Province of practice	
Ontario	18 (50)
Quebec	6 (17)
British Columbia	3 (8)
Manitoba	3 (8)
Nova Scotia	3 (8)
Alberta	2 (6)
New Brunswick	1 (3)

Practice patterns regarding thromboprophylaxis

For patients with bladder cancer receiving neoadjuvant chemotherapy, 25 (69%) respondents indicated that they do not routinely recommend pharmacological thromboprophylaxis, including 13 of 16 medical oncologists. Six (17%) physicians recommend prophylaxis if patients are considered high-risk according to a stratification score, and five (14%) recommend prophylaxis for most patients (Figure 2). Reasons provided by the 25 respondents who did not routinely recommend thromboprophylaxis included 10 (40%) who defer the decision to another physician, eight (32%) who do not believe there is evidence to support thromboprophylaxis in this setting, and four (16%) who are concerned about the risk of bleeding (Figure 3). The four respondents concerned about bleeding were all medical oncologists and nine of the 10 physicians deferring the decision to another physician were urologic oncologists. Similar responses and rationales were observed concerning thromboprophylaxis practice patterns in patients with bladder cancer receiving chemotherapy in the metastatic setting, with 27 (75%) not routinely recommending prophylaxis, six (17%) recommending prophylaxis for high-risk patients, and three (8%) recommending prophylaxis for most.

Need for additional research

Most respondents, 28 (78%), believe that further studies are required to evaluate the risk of VTE in patient receiving chemotherapy for bladder cancer. Moreover, 32 (89%) believe that a randomized clinical trial is needed to determine the efficacy and safety of pharmacological thromboprophylaxis vs. placebo in patients with bladder cancer receiving neoadjuvant chemotherapy. Thirty (83%) respond-

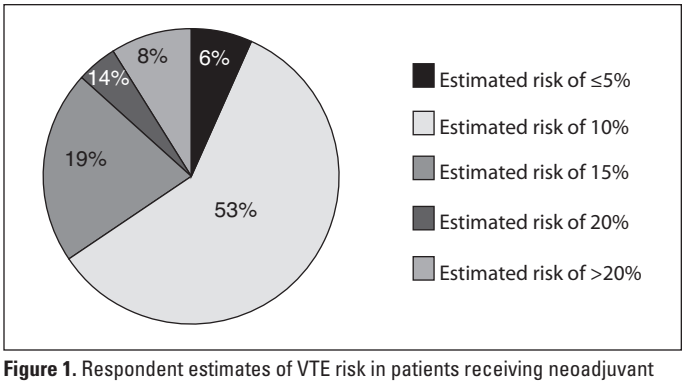

Figure 1. Respondent estimates of VTE risk in patients receiving neoadjuvant chemotherapy for bladder cancer (36 respondents). VTE: venous thromboembolism.

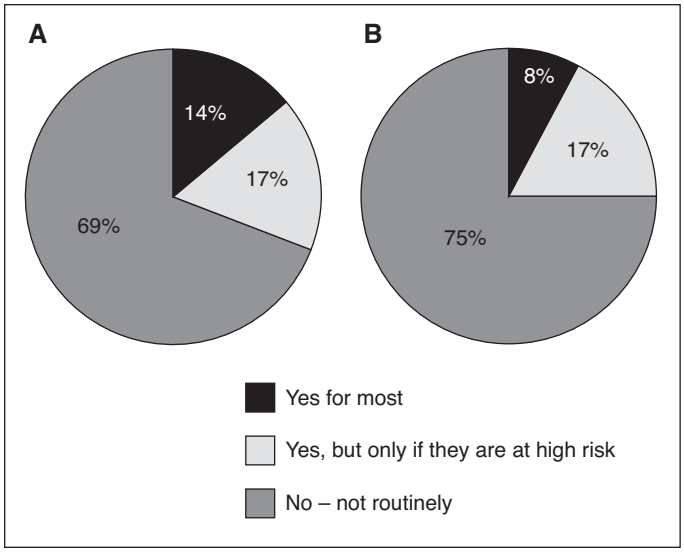

Figure 2. Physicians' practice patterns regarding recommending thromboprophylaxis for **(A)** patients with bladder cancer receiving neoadjuvant chemotherapy; and **(B)** receiving chemotherapy for metastatic disease.

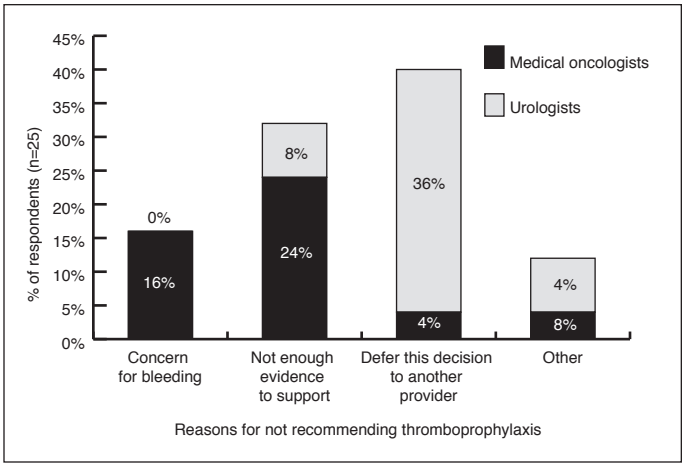

Figure 3. Reasons reported by physicians who did not routinely recommend thromboprophylaxis to patients receiving neoadjuvant chemotherapy.

ents indicated they would recommend thromboprophylaxis if a randomized trial were to demonstrate a 60% reduction in VTE risk with an absolute 1% increase in risk of bleeding. There was strong interest among respondents to participate in thromboprophylaxis trials, with 34 (94%) indicating that they would consider participating. Furthermore, 24 (67%) recommended including both patients receiving either neoadjuvant chemotherapy for localized disease or chemotherapy for metastatic disease in a clinical trial.

Discussion

This study aimed to evaluate practice patterns and perceptions of Canadian urologic oncologists and GU medical oncologists concerning thromboprophylaxis for patients with bladder cancer receiving chemotherapy. We found that almost all respondents believe the risk of VTE during chemotherapy for bladder cancer exceeds 10%, exceeding a threshold of risk for which prophylaxis is usually recommended.[4] Despite acknowledging a very high risk, less than one-third of respondents routinely recommend thromboprophylaxis to their patients, mostly because there is felt to be a lack of evidence, concerns about bleeding, or a deferral of the decision to another physician. Almost all respondents believed that additional studies of thromboprophylaxis in the bladder cancer population are needed.

VTE risk in patients with cancer receiving systemic therapy can be estimated in several ways. The most commonly used and validated tool is the Khorana score.[4] This score categorizes patients into low- (score 0), intermediate- (score 1–2), and high-risk (score ≥3) categories, associated with a three-month VTE risk of 0.8%, 1.8%, and 7.1%, respectively.[4] Notably, in the Khorana score, all patients with bladder cancer have at least intermediate risk because a bladder cancer diagnosis is attributed one point, as prior studies have shown these patients are at elevated risk compared to most cancer patients.[4,11] Guidelines from major organizations, such as ASH, recommend thromboprophylaxis for patients who fall into the high-risk category on the Khorana score and suggest considering prophylaxis for intermediate-risk patients.[11]

In this survey, almost all respondents believed that patients with bladder cancer receiving chemotherapy have a VTE risk that exceeds the high-risk Khorana score group. One large, multicenter study including over 700 patients with bladder cancer (including many Canadian patients) confirmed this perception, reporting a VTE risk of 14% from the start of neoadjuvant chemotherapy to six months postoperative. Other studies have reported a VTE risk as high as 35% in the same population.[14-17] Despite this, 75% of respondents in this survey do not routinely recommend thromboprophylaxis for this patient population. Therefore, it appears perceived risk and clinical practice patterns diverge from one another. Reasons identified in this survey for this disconnect include: uncertainty about how to apply existing evidence to patients with bladder cancer, deferring the decision to other providers (response of most urologic oncologists), and concerns about bleeding.

Previous reports indicate use of neoadjuvant chemotherapy in Canada have increased over time. Although contemporary population-level practice patterns have not been reported, an Ontario-based study reported the uptake of neoadjuvant chemotherapy among 5582 patients who had undergone cystectomy increased from 4% to 27% between 1994 and 2008.[18] A more recent study on 165 patients who underwent cystectomy at one tertiary Canadian center reported that 77

(46.7%) patients received neoadjuvant chemotherapy from January 2016 to April 2020.[19] These increasing rates reflect current guidelines and education, and indicate the results of this survey will impact great number of patients.

Two recent randomized controlled trials, AVERT and CASSINI, established the role of thromboprophylaxis with a DOAC in ambulatory cancer patients with Khorana score ≥2 receiving systemic therapy. The AVERT trial randomized 574 patients to apixaban or placebo and reported that apixaban significantly reduced the risk of VTE from 10.2% to 4.2% (HR 0.41, 95% confidence interval [CI] 0.26–0.65),[10] corresponding to a number needed to treat of 17. The CASSINI trial randomized 841 patients to rivaroxaban or placebo and found that rivaroxaban reduced the risk of VTE from 6.4% to 2.6% (HR 0.4, 95% CI 0.2–0.8) during treatment.[9] Despite these findings, our survey indicates that physicians may not be familiar with this evidence or may feel the results are not generalizable to the bladder cancer population. Indeed, there were only five patients with bladder cancer in the AVERT trial and 32 with GU cancers (bladder, testis, ureter, kidney) in the CASSINI trial, comprising 1% and 3.8% of the respective study populations.[9,10] Notably, 83% of respondents indicated they would recommend thromboprophylaxis if a 60% reduction in VTE events was demonstrated in patients with bladder cancer (the same risk reduction reported by AVERT and CASSINI).

Another concern for initiating thromboprophylaxis for patients with bladder cancer is bleeding (16% of respondents). The AVERT trial reported a 2.1% risk of major bleeding with apixaban compared to 1.1% with placebo (HR 1.89, 95% CI 0.39–9.24).[10] Similarly, the CASSINI trial reported a 2% risk of major bleeding with rivaroxaban compared to 1% with placebo (HR 1.96, 95% CI 0.59–6.49).[9] Bleeding may be of particular concern in patients with bladder cancer, as trials investigating DOACs as treatment for cancer-associated thrombosis have shown an increased risk of hematuria, likely due to the mucosal-based location of bladder tumors and ability of patients to easily detect bleeding in the urine.[20,21] The AVERT trial reported that bleeding events were mainly due to higher rates of hematuria, gastrointestinal and gynecological bleeding.

The 2021 ASH guideline identified that research studies that assess the role of thromboprophylaxis by specific disease site were a research priority.[11] This designation as a research priority is reflected in our survey, where 89% of respondents indicated they believe a randomized trial is needed to demonstrate efficacy and safety of thromboprophylaxis specifically in the bladder cancer population. Furthermore, we found a great interest of Canadian GU oncologists (94% of respondents) in pursuing and participating in additional research on this topic. Based on these results, our group has designed a randomized controlled for patients with GU cancers initiating systemic therapy and at elevated risk of VTE. The trial will randomize patients to a direct oral anticoagulant or placebo and have a similar design to landmark trials such as AVERT and CASSINI but focused on the GU population. This trial will provide direct evidence addressing the benefit and risks of thromboprophylaxis in bladder cancer and will address the concerns highlighted by respondents of this survey.

Limitations

This study has several limitations to consider.

First, the number of respondents is relatively small. The primary reason for the small sample size is that the advanced bladder cancer population is primarily managed by highly specialized physicians in Canada. We targeted physicians known to have an interest in advanced bladder cancer to ensure an acceptable response rate and reduce respondent bias.

Second, the survey was limited to Canadian GU oncologists who predominantly worked at academic centers, therefore, reported practice patterns may differ from physicians at non-academic centers and in other countries.

Third, while we found that approximately 75% of respondents do not routinely recommend thromboprophylaxis for patients receiving chemotherapy for bladder cancer, a significant number reported deferring the decision to another provider. The proportion of medical oncologists recommending prophylaxis was, however, similar to urologists, indicating the deferral of decisions to another provider likely is not changing the proportion of patients receiving thromboprophylaxis overall.

Conclusions

Patients with bladder cancer receiving chemotherapy have very high risk of VTE but do not routinely receive thromboprophylaxis. We identified a strong desire among Canadian urologic and medical oncologists to participate in a clinical trial of thromboprophylaxis in patients with bladder cancer receiving chemotherapy.

Competing interests: Dr. Carrier reports grants from BMS, Leo Pharma, and Pfizer; personal fees from Bayer, BMS, Leo Pharma, Pfizer, Sanofi, and Servier. Dr. Bossé has received speaker and consultancy fees from AbbVie, Amgen, AstraZeneca, Bayer, BMS, Esai, Ipsen, Merck, and Pfizer. Dr. Wang reports advisory board honoraria from Servier and Valeo; and grants from Leo Pharma. Dr. Morash has been an advisory board member for AbbVie, Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi, and TerSera. Dr. Cagiannos has been an advisory board member for AbbVie; and has received honoraria from Abbvie, Astellas, Bayer, and Ferring. Dr. Lavallée has been an advisory board member for Astellas, Bayer, Ferring, Janssen, Knight, and Sanofi; and has received an education grant (unrelated to the current work) from Sanofi. The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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Correspondence: Dr. Luke T. Lavallée, Division of Urology, The University of Ottawa, Ottawa, ON, Canada; lulavallee@toh.ca