Effect of anticoagulants and antiplatelet agents on the efficacy of intravesical BCG treatment of bladder cancer: A systematic review

Nader Fahmy, MD, PhD, FRCSC;[*] Alejandro Lazo-Langner, MD, MSc;[†] Alla E. Iansavichene, BSc, MLIS;[§] Stephen E. Pautler, BSc, MD, FRCSC[*]

[*]Divisions of Urology & Surgical Oncology, Departments of Surgery & Oncology, Schulich School of Medicine & Dentistry, Western University, London, ON; [†]Department of Medicine, Division of Hematology; and Department of Epidemiology and Biostatistics; and Department of Oncology, Western University, London ON; [§]Library Services, London Health Sciences Centre, London ON

Cite as: *Can Urol Assoc J* 2013;7 (11-12):e740-9. http://dx.doi.org/10.5489/cuaj.1213
Published online November 8, 2013.

Abstract

We performed a systematic review of publications describing a correlation between oral anticoagulant medications and intravesical BCG outcome. We collected information on the impact of such medications on tumour recurrence and progression and we excluded papers not reporting outcome correlations. Patients were divided into group 1 and 2 based on whether they were taking or not taking any anticoagulant medications. A total of 7 manuscripts published between 1990 and 2009 were included in this study. Data heterogeneity precluded meta-analysis. In studies combining all anticoagulant medications, 3 out of 5 (60%) publications did not identify any difference in outcome, while 2 (40%) documented significantly more recurrences in group 1 patients. In studies performing multivariate analysis and only examining the intake of 1 medication, warfarin alone seemed to be associated with increased risk of bladder tumour recurrences and progression following intravesical BCG treatment, while ASA alone seemed to be associated with more protective effects. There is no strong evidence to support the allegations of a protective role of ASA and a deleterious role for warfarin. Further, well-designed experimental and clinical studies are needed to clarify the mechanism of action of intravesical BCG along with possible drug interactions.

Introduction

Bladder cancer is the sixth most common non-cutaneous cancer and the ninth most common cause of overall cancer death in Canada.[1] Eighty percent of urothelial cancers present as non-invasive disease. Transurethral resection of bladder tumours (TURBT), along with intravesical Bacillus Calmette-Guérin (BCG) management, is presently considered the most effective management for intermediate and high-risk non-invasive tumours. Despite a significant reduction in recurrence and progression rates following BCG, still up to 40% of patients will not respond and up to 50% may even progress.[2,3] Consequently, studies have attempted to define factors that may influence BCG success.

The precise mechanism of BCG antitumour response remains undefined. BCG binding to the extracellular matrix was documented to be a key step in the initiation of its antitumour response.[4,5] In experimental studies, medications that inhibit fibrin clot formation have significantly decreased its antitumour activity,[4] while antifibrinolytic medications improved its outcome.[6,7]

A concern regarding the efficacy of intravesical BCG administration thus emerges when taking into account that urothelial cancers are more common in older patients who often have a significant history of vascular diseases and are frequently taking systemic anticoagulants or antiplatelet agents. Multiple publications have tested the outcome of BCG in patients receiving anticoagulant medications with variable results.

The goal of the current study was to perform a systematic review of the literature to determine if administering intravesical BCG in patients on oral anticoagulant or antiplatelet medications affects the prognosis.

Methods

A systematic review was performed in conformity to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[8]

Finding relevant studies

We systematically searched MEDLINE (1946 to January 2013) using both Ovid SP and PubMed search interfaces, EMBASE (1974 to Week 1, 2013), BIOSIS Previews (January 2013), Web of Science with Conference Proceedings (January 2013), and the Cochrane Central Register of Controlled Trials

(January 2013) databases; we looked for studies assessing the effect of anticoagulants and antiplatelet agents on the efficacy of BCG intravesical therapy in patients with bladder cancer. We used various combinations of subject headings and text words, such as BCG vaccine, Bacillus Calmette-Guérin, anticoagulants, antiplatelet, antiaggregant, platelet aggregation inhibitors, blood platelets, platelet aggregation, warfarin, acetylsalicylic acid, clopidogrel, fibrin clot inhibitor, urinary bladder neoplasms, transitional cell carcinoma (TCC), urothelial cell carcinoma (UCC), bladder cancer, bladder neoplasm, and bladder tumour.

The search strategies were modified for each electronic database using database-specific search terms, field names and syntax. In addition, the bibliographies of relevant publications, internet-based registry of clinical trials (clinicaltrials.gov), Health Technology Assessment (HTA) agencies, Google and Google Scholar were also searched to identify additional citations and ongoing trials. We excluded papers in languages other than English.

Criteria for considering articles for review

Studies were included if they met the following criteria: (1) the article involves patients with bladder tumours managed with an intravesical BCG instillation; (2) the study entails a cohort of patients who are on at least one oral anticoagulant or antiplatelet medication; and (3) the manuscript included information on prognosis.

For publications studying the outcome of different management modalities, if shown, only data concerning outcome of intravesical BCG instillation was included. Since the goal of this study was to assess association of oral anticoagulant or antiplatelet medication in BCG treated patients with prognosis, all papers not reporting any outcome correlations were excluded. Manuscripts involving anticoagulant medications administered by routes other than orally (e.g., intravesically) were also excluded.

Relevant data were extracted into predesigned custom-made spreadsheets. If available, the outcomes related to a single distinct anticoagulant or antiplatelet medications were extracted separately. Studies were assessed for inclusion by 1 reviewer and corroborated by 2 other independent reviewers. Differences were resolved by consensus.

For descriptive purposes, the cohort of patients taking an anticoagulant or antiplatelet medication was labelled group 1 and those not on an anticoagulant or antiplatelet medication were called group 2.

The primary endpoint was tumour recurrence. The secondary endpoints were (1) recurrence stage and/or grade; (2) tumour progression; and (3) disease-free interval (time to recurrence or progression).

Statistical analysis

A formal meta-analysis was not conducted due to the heterogeneity amongst the publications regarding the reported study populations, oral anticoagulants or antiplatelet drugs used, tumour pathologies, BCG regimens and outcomes. Data were extracted and summarized using central tendency measures and ranges as provided by the authors.

Results

Search results and characteristics of included studies

We identified 375 citations; after removing duplicate citations, 311 records were assessed for relevance. In total, 303 records were excluded. One pertinent record that was only published as a conference abstract was also excluded.[9] In total, 7 studies met the inclusion criteria (Fig. 1) and were included in this analysis. Four (57%) of these studies were North American,[10-13] 2 (29%) Australian[14,15] and one (14%) European.[16] These papers described investigations conducted between 1981 and 2006 and were published between1990 and 2009. For all manuscripts, the outcome analysis in relation to fibrin clot inhibitors was computed retrospectively. The included studies featured a total of 1423 patients with primary or recurrent bladder urothelial carcinoma treated with intravesical BCG. None of the publications included patients with upper tract urothelial carcinoma. They involved 341 patients on at least 1 anticoagulant or antiplatelet medication (Group 1).

Baseline patient characteristics and study endpoints for all studies are shown in Table 1; medication history, tumour characteristics and BCG information are in Table 2.

While 5 studies[10,13-16] combined the outcome of different medications taken either separately or together (Table 3), only 3 articles[10-12] tested the outcome of only 1 type of anticoagulant or antiplatelet medication (Table 3, Table 4). All manuscripts reported tumour recurrence following intravesical BCG. Tumour progression was evaluated in 3 studies.[10,11,13] Multivariate analyses was only performed in 3 studies[10-12] (Table 3, Table 4).

Effects of anticoagulant or antiplatelet medications on tumor recurrence

Studies combining patients on multiple anticoagulant or antiplatelet medications taken either separately or together

Two studies[14,15] documented significantly higher overall tumour recurrence rates in Group 1. One study[16] showed a non-significant tendency towards more recurrences in Group 2 patients, while 2 other manuscripts did not show differences among both groups[10,13] even after controlling for

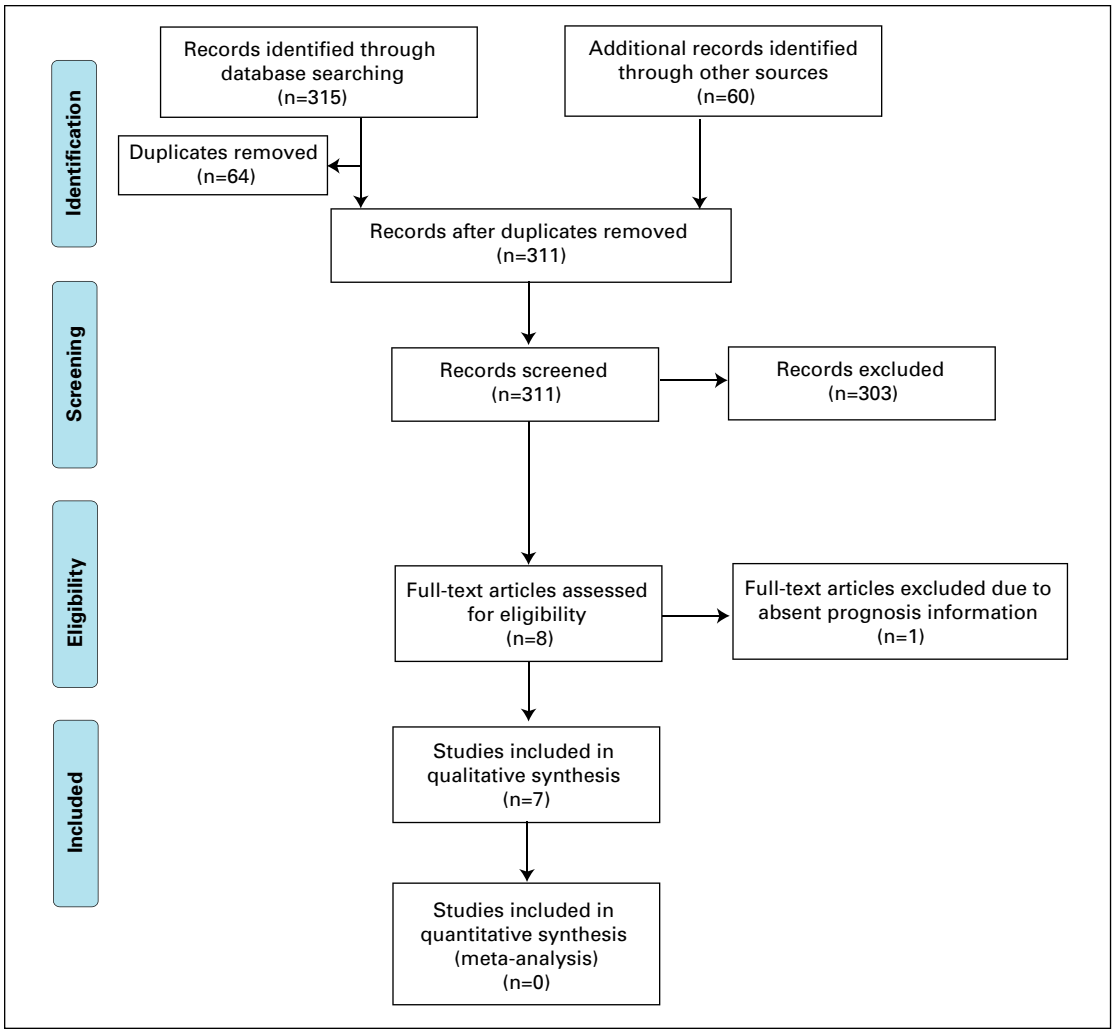

Fig. 1. PRISMA Study Selection Flow Diagram. Adapted from Moher et al.[8]

the type of anticoagulant or antiplatelet medication used.[10] When excluding tumour progression from overall recurrences, 1 of the 2 latter studies[13] revealed a significantly increased rate of superficial tumour recurrences in Group 1 patients. Time to recurrence was assessed in 2 studies[10,16] and was not significantly different between both groups (Table 3).

Studies assessing patients taking only one type of anticoagulant or antiplatelet medication

For patients taking oral warfarin alone, 1 study did not document any difference in recurrence and in time to recurrence among both groups by univariate analysis.[10] In 2 studies using multivariate analyses, warfarin intake alone was associated with significantly increased risks of recurrences in Group 1 patients following intravesical BCG treatment.[10,12] In patients taking only systemic acetylsalicylic acid (ASA), by means of univariate analysis, 1 study reported significantly higher risk of tumour recurrence in Group 2 patients,[11] whereas another study did not.[8] When using multivariate analyses, 1 study documented evidence of significantly decreased risk of recurrence within Group 1 patients after controlling for age, sex, smoking status, maintenance BCG, and the presence of carcinoma in situ (CIS) or papillary tumour.[11] Another study however failed to show any significant difference in recurrence rates among both groups after controlling for age, initial tumour stage (superficial vs. invasive), and anticoagulation medication used.[10]

Effects of anticoagulant or antiplatelet medications on tumour progression

Studies combining patients on multiple anticoagulant or antiplatelet medications taken either separately or together

There was neither a significant difference in tumour progression nor in time to progression in both groups when tested by univariate analyses.[10,13]

Table 1. Baseline patient characteristics, study design and study endpoints

	Hudson et al.[13] 1990	P'ng et al.[15] 1993	Witjes et al.[16] 1993	Rogerson[14] 1994	Heiner et al.[12] 2008	Gee et al.[11] 2008	Boorjian et al.[10] 2009
Study years included	Dec 1981-June 1989	1985-1990	Apr 1987-Dec 1991	Dec 1987-Oct 1991	Dec 1999-July 2004	June 1991-Sep 2003	July 1978-Nov 2006
Study type	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Institution	- Washington university - Jewish hospital of St Louis	- Royal Brisbane Hospital - Princess Alexandra Hospital	- Dutch Southeast Cooperative Urological Group	Heidelberg Repatriation Hospital	- Augusta Veterans Affairs Medical Center - Medical College of Georgia	- University of Wisconsin Hospital and Clinics	- Memorial Sloan Kettering Cancer Center
Province/country	Missouri, USA	Queensland, Australia	Netherlands	Victoria, Australia	Georgia, USA	Wisconsin, USA	New York, USA
Total patients	162	45	313	56	58	154	1218
Included patients	149	45	183	38	58	43	907
Inclusion selection criteria	Available medication record	All patients included	N/A	Available medication record	N/A	Available records	- Available records, - No prior surgical intervention - >1990
Anticoagulant G1	29	9	42	13	7	20	221
Control G2	120	36	141	25	51	23	686
Male:Female ratio Statistical significance	N/A	33:12	N/A	N/A	N/A	36:7 More males in G1 (NS)	721:186 More males in G1 ($p < 0.01$)
Age, years (range) Statistical significance	N/A	Mean both groups: 69 (36-92)	N/A	N/A	N/A	Mean - G1: 72 - G2: 63 $p < 0.01$	Median - G1: 69 - G2: 65 $p < 0.01$
Follow-up (range)	Mean - G1: 26.5 months - G2: 29.8 months	Mean both groups 20.3 months Median both groups 16 months (3-56)	Mean - G1: 22.5 months (4.4-49.5) - G2: 20.8 months (2.6-53.2)	Mean varied among stages ranging from 6 to 28 months (2-36)	N/A	N/A	Median 4.2 years in patients without recurrence and 3.7 years without progression
Primary endpoint studied	Tumour recurrence	Persistent or recurrence tumour at first follow-up in 3 months	Disease (recurrence) free interval	Persistent or recurrence disease at 6 weeks	Response to therapy categorized in relation to age - 1: (complete) - 2: (recurrence at increase interval or dec. grade/stage - 3: (recurrence same interval or same stage/grade) - 4: (recurrence shorter interval or higher stage/grade)	Recurrence-free and progression-free intervals	Tumour recurrence and progression to open surgery

G: group; N/A: not available

Table 2. Medication history, tumour characteristics and BCG information

		Hudson et al.[13] 1990	P'ng et al.[15] 1993	Witjes et al.[16] 1993	Rogerson[14] 1994	Heiner et al.[12] 2008	Gee et al.[11] 2008	Boorjian et al.[10] 2009
	Gp1/Gp2	**29/120**	**9/36**	**42/141**	**13/25**	**7/51**	**20/23**	**221/686**
Medication history	Anticoagulant medication used in G1	- Warfarin (n=1) - ASA (n=21) - Dipyridamole (n=7) - Indomethacin (n=4) - Ibuprofen (n=3)	- Warfarin (n=1) - ASA (n=4) - NSAID (n=4)	- Warfarin (n=15) - ASA (n=18) - Dipyridamole (n=4) - Indomethacin (n=2) - Naproxen (n=1) - Ibuprofen (n=3) - Diclofenac (n=4)	- NSAIDs (n=13)	- Warfarin (n=7)	ASA (n=20)	- Warfarin (n=52) - ASA (n=170) - Clopidogrel (n=34)
	Other concomitant medications	Antibiotics, CVS, respiratory, DM, CNS, GIT, steroids, thyroid, vitamins, antihistaminics	Unknown, No Antibiotics	Antibiotics (more significant in G1), CVS, CNS, respiratory, paracetamol and others	N/A	N/A	N/A	N/A
Tumour characteristics	Primary/ recurrent urothelial carcinoma	Primary or recurrent	N/A	Primary or recurrent	Primary or recurrent	N/A	N/A	N/A
	pT stage	CIS, pTa, pT1, G1: 24%, 38%, 38% G2: 22%, 42%, 36% - No stats	CIS, pTa, (not stratified by anticoag. gps)	CIS, pTa, pT1 G1: 9%, 60%, 31% G2: 11%, 64%, 25% - No stats	CIS, pTa, pT1,p T4 (not stratified by anticoag. group) [1 pt had history of pT2, treated with ERT and rec as T1)	CIS , pTa, pT1 (not stratified by anticoag group)	CIS, pure papillary bladder cancer G1: 75%, 40% G2: 91%, 13% - Non-significant	Stages imputed as: - [pTa, pT1, CIS] - [pT2, pT3] - Unknown G1: 69%, 2%, 29% G2: 70%, 5%, 26% - No stats
	Grade	Grade I, II, III G1: 17%, 69%, 14% G2: 21%, 63%, 16%	Grade I, II, III (not stratified by anticoagulant groups)	N/A	N/A	N/A	N/A	Grades imputed as: Low, high and unknown G1: 9%, 50%, 42% G2: 13%, 48%, 39%

*G: group; TICE: Merck & Co. Inc., Whitehouse Station, NJ; ±RIVM: A Dutch BCG preparation. BCG: Bacille Calmette-Guérin; ASA: acetylsalicylic acid; NSAID: nonsteroidal antiinflammatory drugs; CVS: cardiovascular; DM: diabetes mellitus; CNS: central nervous system; GIT: gastrointestinal tract; N/A: not available; CIS: carcinoma in situ.

Studies assessing patients taking only one type of anticoagulant or antiplatelet medication

Among patients taking oral warfarin alone, using both univariate and multivariate analyses, 1 study indicated significantly higher progression risk in Group 1 patients with a shorter median time to progression.[10] In patients taking only systemic ASA, using univariate analyses, 1 study indicated no difference in tumour progression among both groups,[11] while another study documented significantly decreased risk of progression among Group 1 patients.[10] On multivariate analysis, only 1 study reported a significantly decreased risk of progression to open surgery following intravesical BCG instillation in patients taking ASA.[10]

Discussion

Along with TURBT, intravesical BCG has become a common treatment to manage intermediate- and high-risk non-invasive bladder cancer. Intravesical BCG was shown to

Table 2. Medication history, tumour characteristics and BCG information (cont'd)

		Hudson et al.[13] 1990	P'ng et al.[15] 1993	Witjes et al.[16] 1993	Rogerson[14] 1994	Heiner et al.[12] 2008	Gee et al.[11] 2008	Boorjian et al.[10] 2009
BCG information	BCG strain	Pasteur	Pasteur strain	TICE* (n=25) and RIVM± (n=17)	Pasteur strain	TICE*	N/A	N/A
	Dose Dilution Time in Bladder	120 mg in 50 cc normal saline 2 hours	120 mg in N/A N/A	5×10^8 in 50 cc normal saline N/A	60 mg or 120 mg in 60 cc normal saline 1.5 hours	50 mg in 50 cc normal saline N/A	N/A N/A N/A	N/A N/A N/A
	Interval given post-TURBT	within 6 months	N/A	7 to 15 d	N/A	N/A	N/A	N/A
	Course induction cycle	- 45 had 6 or 12 week initial BCG course -104 had 1 or more 6 week BCG courses	1/week × 6 weeks	- 1/week × 6 weeks - 14% G11 and 17% G2 had a second 6-week course	- 1/week × 6 weeks - Some patients received a second course	1/week × 6 weeks	N/A	1/week × 6 weeks
	Maintenance BCG	N/A	N/A	N/A	N/A	- If no progression –>3 weekly treatments for 3 years - Some patients recruited while on maintenance	Not all patients G1: 3 (15%) G2: 6 (26%)	N/A
	BCG complications	N/A	N/A	Bacterial cystitis G1>G2	Not stratified by anticoagulant group	- G1: 1/7 (14.3%) - G2: 4/17 (36.2%)	N/A	N/A

*G: group; TICE: Merck & Co. Inc., Whitehouse Station, NJ; ±RIVM: A Dutch BCG preparation. BCG: Bacille Calmette-Guérin; ASA: acetylsalicylic acid; NSAID: nonsteroidal antiinflammatory drugs; CVS: cardiovascular; DM: diabetes mellitus; CNS: central nervous system; GIT: gastrointestinal tract; N/A: not available; CIS: carcinoma in situ.

significantly decrease tumour recurrence and progression when compared to TURBT alone. Still, up to 40% of patients receiving intravesical BCG failed to respond and as high as 50% of patients even progressed.[2,3] Thus, it becomes intuitively evident to try and examine potential risks influencing BCG treatment success.

The exact mechanism by which BCG creates its response remains unclear. It may be achieved through several mechanisms.[17] TURBT initially exposes the lamina propria and basement membrane of the urothelium leading to fibrin clot formation, altogether rich in fibronectin. The live attenuated strain of Mycobacterium bovis can thus adhere to the newly exposed fibronectin and undergo endocytosis resulting into a massive release of cytokines, chemokines and leads to activation of natural killer cells and cytotoxic T lymphocytes.[18] This BCG-fibronectin binding capacity directly correlates with BCG anti-tumor activity.[19] This key role of fibronectin in initiating an antitumour response was documented in a murine model, when administering anti-fibronectin antibodies lead to a total loss of BCG anti-tumour activity.[4] Likewise, intravesical heparin administration inhibited BCG-fibronectin binding in a rabbit model.[7] Conversely, antifibrinolytic agents given intravenously[6] or intravesically[7] significantly improved BCG antitumour responses in experimental models. It was thus postulated that medications inhibiting fibrin clot formation would adversely influence BCG efficacy. Based on these findings, antifibrinolytic agents were administered intravesically (to prevent their systemic adverse effects) in a randomized prospective double blinded controlled study including 257 non-invasive low- to intermediate-risk bladder cancer patients. This study reported significantly favourable outcomes on a short median follow-up of 2 years.[20]

Since bladder tumours are more common in older patients who frequently suffer from cardiac and/or cerebrovascular diseases and are often dependent on anticoagulant or antiplatelet medications, the efficacy of intravesical BCG in these patients has been questioned. Therefore, we systematically reviewed the literature to try and identify if concomitant intake of anticoagulant/antiplatelet medications affects the prognosis of intravesical BCG. For descriptive analyses, patients were divided into Groups 1 and 2 based

Table 3. Studies combining the outcome of different anticoagulant or antiplatelet medications

	Hudson et al.[13] 1990	P'ng et al.[15] 1993	Witjes et al.[16] 1993	Rogerson[14] 1994	Heiner et al.[12] 2008	Gee et al.[11] 2008	Boorjian et al.[10] 2009
G1/G2 Medication	**29/120 Combined**	**9/36 Combined**	**42/141 Combined**	**13/25 Combined**	**7/51 Warfarin**	**20/23 ASA**	**221/686 Combined**
- Recurrence in G1	-15/29 (52%)*	- 8/9 (88.9%)	- 13/42 (31%)*	- 11/13 (84.6%)*	- N/A	- 8/20 (40%)*	- 189/221 (85.5%)*
- Time to recurrence (range)	- N/A	- NA	- Mean: 9.7 months** (2.9-20.4)	- N/A	- N/A	- 5-year risk: 36%*	- Median: 7 months*
- Progression or recurrence stage/ grade	- 10/29 (35%)** superficial or CIS - 5/29 (17%) invasive or metastasis	- N/A	- N/A	- N/A	- N/A	- 4/20 (20%)** (stages not shown)	- 80/221 to open surgery* (stages not shown)
- Time to progression	- N/A	- N/A	- N/A	- N/A	- N/A	- N/A	- 5-year risk: 40%*
- Recurrence in G2	- 40/120 (33%)*	- 11/36 (30.6%)*	- 56/141 (40%)*	-12/25 (48%)*	- N/A	- 17/23 (74%)*	- 566/686 (82.5%)*
- Time to recurrence (range)	- N/A	- NA	- Mean: 9.4 months** (2.4-43.4)	- N/A	- N/A	- 5-year risk: 73%*	- Median: 6 months*
- Progression or recurrence stage/ grade	-10/120 (8%)** recurrence as superficial/ CIS - 30/120 (25%) recurrence as invasive or metastasis	- N/A	- N/A	- N/A	- N/A	- 7/23 (30%)** (stages not shown)	- 270/686 to open surgery* (stages not shown)
-Time to progression	- N/A	- N/A	- N/A	- N/A	- N/A	- N/A	- 5-year risk: 43%*
Statistical Tests:	Chi square test	Fisher's exact test	Kaplan-Meier/log-rank test	Chi-square test	- N/A	Kaplan-Meier/ log-rank test	Kaplan-Meier/ log-rank test
p value	$*p = 0.065$ $**p < 0.01$	$*x^2 = 7.79$, $*p < 0.01$	$p = 0.28$ (NS)	$*p < 0.05$		$*p = 0.03$ $**p = 0.4$ (NS)	$*p = 0.6$ (NS)
Univariate results summary	- NS difference in overall recurrences - Significantly more superficial bladder tumour recurrence in G1	- Significantly more recurrence in G1	- **NS more failure in G2 - NS time to failure	- Significantly more recurrence in G1	- N/A	- Significantly more recurrence in G2 - NS difference in progression	- NS difference in median time to recurrence or progression in 2 groups

Asterisks indicate data used for *p* value calculations.
G: group; BCG: Bacille Calmette-Guérin; ASA: acetylsalicylic acid; CIS: carcinoma in situ; N/A: not available; NS: non-significant; HR: hazard ratio; ANOVA: analysis of variance.

Table 3. Studies combining the outcome of different anticoagulant or antiplatelet medications (cont'd)

	Hudson et al.[13] 1990	P'ng et al.[15] 1993	Witjes et al.[16] 1993	Rogerson[14] 1994	Heiner et al.[12] 2008	Gee et al.[11] 2008	Boorjian et al.[10] 2009
G1/G2 Medication	**29/120 Combined**	**9/36 Combined**	**42/141 Combined**	**13/25 Combined**	**7/51 Warfarin**	**20/23 ASA**	**221/686 Combined**
Multivariate analyses results							
- Recurrences	N/A	N/A	N/A	N/A	- Sig. increased risks in Gp. 1 - Average rank 2.6 - $p < 0.01$	- Significant decreased risk in G1 - HR: 0.179 (0.062-0.516) p = 0.001	N/A
- Progression	N/A	N/A	N/A	N/A	N/A	N/A	N/A
- Statistical tests - Controlled covariates	N/A	N/A	N/A	N/A	- ANOVA - Controlling for age and BCG complications	- Multivariate analysis - Age, sex, smoking, maintenance BCG, CIS and presence of papillary tumour	N/A

Asterisks indicate data used for p value calculations.
G: group; BCG: Bacille Calmette-Guérin; ASA: acetylsalicylic acid; CIS: carcinoma in situ; N/A: not available; NS: non-significant; HR: hazard ratio; ANOVA: analysis of variance.

Table 4. Study reporting the outcome of ASA or warfarin intake alone in a subgroup cohort

			Boorjian et. al.[10] 2009	
		G1/G2 Anticoagulant	**170/737 ASA**	**52/855 Warfarin**
Univariate analyses using Kaplan-Meier / log-rank test		- Recurrence in G1	- N/A	- N/A
		- Time to recurrence (range)	- Median: 7 months*	- Median: 7 months*
		- 5-year risk of recurrence	- N/A	- N/A
		- Progression	- N/A	- N/A
		- Time to progression	- N/A	- Median: 2.1 years
		- 5-year risk of progression	- 34%**	- 65%**
		- Recurrence in G2	- N/A	- N/A
		- Time to recurrence (range)	- Median: 6 months*	- Median: 6 months*
		- 5-year risk of recurrence	- N/A	- N/A
		- Progression	- N/A	- N/A
		- Time to progression	- N/A	- Median: 9 years
		- 5-year risk of progression	- 44%**	- 41%**
		p value	*p = 0.6 (NS) **p = 0.029	*p = 0.14 (NS) **p = <0.01
		Results summary:	- Similar recurrence in both groups - Sig. more prog. in Gp2.	- Similar recurrence in both groups - Significantly more progression in G1
Multivariate analyses	Recurrence	Impact of 1 anticoagulant medication in a cohort of patients taking any 1 or more anticoagulant	- NS difference among both groups - HR: 0.91 (0.75- 1.10) - p = 0.3	- NS difference among both groups - HR: 1.19 (0.89-1.59) - p = 0.2
		Impact of 1 anticoagulant medication in a cohort of patients only taking 1 anticoagulant	- NS difference among both groups (data not shown)	- Significantly increased risks in G1 - HR: 1.39, 95% CI (1-1.94) - p = 0.047
	- Progression		- Significantly decreased risk of progression to open surgery - HR: 0.71, 95%CI (0.52-0.96) - p = 0.024	- Significantly increased risks in G1 - HR: 1.89, 95% CI (1.31-2.74) - p = 0.0007
	- Statistical tests		- Cox proportional hazards regression model	
	- Controlled covariates		- Age, initial tumour stage (superficial vs. invasive) and anticoagulation medication used	

Asterisks indicate data used for p value calculations. N/A: not available; NS: non-significant; G: group; HR: hazard ratio; CI: confidence interval.

on whether they were taking anticoagulant or antiplatelet medications or not, respectively.

The ideal method to test our outcomes is to design randomized, controlled prospective studies. However, if no randomized studies exist, observational studies showing consistent results can still be used to reasonably draw valid conclusion; there is a caveat: if such studies are retrospective and inadequately conducted, they are prone to inherent selection biases.

Given the heterogeneity of these studies we could not perform a meta-analysis. Reviewing the literature has revealed significant differences:

1. Failure to reveal critical baseline patient characteristics;
2. Limited number of study patients;
3. Exclusions of up to more than half of patients due to unavailability of medication records;
4. Different mean age among tested groups;
5. Different duration and follow-up schedules;
6. Different use of anticoagulant or antiplatelet medication type, dosage and duration;
7. Combining the outcome of different anticoagulant or antiplatelet medications groups whether taken separately or together;
8. Failure to take into account the concomitant intake of other medications;
9. Diverse risk factors for bladder cancer prognosis;
10. Different pre-treatment tumour stages and grades;
11. Variable BCG strains used along with multiple BCG regimens;
12. Unavailability of BCG complications;
13. Unknown recurrence stage and grade;
14. Different tested endpoints using variable statistical analyses; and
15. An ill-defined time to recurrence with possible introduction of lead time biases.

Despite all these differences, most investigators did not control for the vast variation in their examined variables. Among those studies that performed univariate analysis, 5 combined the different groups of anticoagulant or antiplatelet medications.[10,13-16] Only 1 manuscript tested individual recurrences based on invasion stage and reported more superficial recurrences in group 1 patients.[13] However, most publications only compared overall recurrences and 60% of the studies failed to show any statistical difference in disease recurrence among both groups.[10,13,16] The conference abstract that was excluded from this study also failed to show any significant difference in recurrence-free survival rates following antiplatelet administration.[9] Two studies examined tumour progression following BCG and both found no differences among both groups.[10,13]

Only 2 published manuscripts reported the outcome of patients taking oral warfarin alone. One of the studies used multivariate analyses in a cohort of patients taking 1 or more anticoagulant medications and did not find any significant difference in recurrence rates among both groups after controlling for the type of anticoagulant medication used. It was only when the authors sub-selected a cohort (using only 1 anticoagulant medication) and compared those to a group of controls that a significantly increased risk of recurrence following BCG was found among patients on warfarin (Table 4).[10] Such analytical strategy raises serious concerns regarding the possibility of selection bias.

This manuscript had further limitations some of which were acknowledged by the authors, given the difficult nature of conducting and planning such studies. These limitations involved combining pTa, pT1 and CIS tumour stages that are known to have dissimilar risks and prognosis under one category. It also included the inclusion of a significant proportion of patients with unknown stage and grade. Furthermore authors did not control for other important risk factors, like smoking history and duration of warfarin medication use. Moreover these patients never received a maintenance intravesical BCG.

Similarly, another study compared the outcome of warfarin intake alone by ranking the response to BCG therapy into an ordinal scale of 1 to 4 and averaging those responses.[12] The authors reported a poorer response rank of 2.6 following BCG in patients on warfarin independent of age. This study also had many limitations, including drawing conclusions from only 7 patients in the warfarin group and not controlling for all of the other risk factors. Furthermore, these scale numbers represent a rank with no numerical measurable differences between groups, thus computing means becomes very confusing and caution should be taken prior to drawing conclusion from such statistical analysis. Additionally, analysis of variance (ANOVA) for such categorical values may lead to misleading results that go beyond the normal chance of Type I and Type II errors.[21]

By means of multivariate analyses, 2 publications tested intravesical BCG outcome in patients only taking ASA and both described a seemingly protective effect.[10,11] While 1 study reported significantly fewer recurrences with no difference in progression in patients taking ASA,[11] the other manuscript failed to find any significant difference in recurrence and found a significantly decreased risk of progression to open surgery in the ASA group.[10] Several mechanisms have been suggested to elucidate the possible ASA beneficiary effects.[10] It may be in part explained by the fact that local or systemic anticoagulants may prevent tumour cell adhesion and implantation to injured urothelium.[22,23] Furthermore, ASA may exert its protective role through its non-selective cyclooxygenase (COX)-2 inhibition. COX-inhibiting drugs have antitumour activity in both canine and rodent models of urinary bladder cancer.[24] Additionally COX-2 was found to be expressed in human CIS and invasive urothelial carcinoma, but not in the normal bladder.[24] Moreover, COX

inhibition in a murine model enhanced the production of interleukin-12 by BCG activated dendritic cells and generated type 1 T-helper response that may partially justify the improved BCG efficacy.[25]

The limitations of this study are similar to those in previously published studies. This study highlights the fact that our cumulative understanding in this area is very limited and insufficient to justify the practice of discontinuing warfarin prior to intravesical BCG therapy. We also suggest that patients continue their ASA medications for their cardiovascular benefits rather than for any other potential benefits in changing the prognosis of their bladder cancer.

Conclusions

A total of 7 published manuscripts examined the outcome of intravesical BCG in patients receiving anticoagulant or antiplatelet medications with contradictory results. Based on published data, there is no strong evidence to either encourage or discourage anticoagulant or antiplatelet medications while on intravesical BCG therapy yet. Further experimental and properly conducted clinical studies are still needed to further explore drug interactions and elucidate the mechanism of action of BCG.

Competing interests: Dr. Lazo-Langner has received honoraria for Advisory Board membership from Pfizer and LeoPharma. He has also received an unrestricted educational grant and honoraria from Alexion and Pfizer. He has participated in clinical trials for Pfizer, LeoPharma, Bayer and Daiichi-Sankyo. Dr. Fahmy, Ms. Iansavichene and Dr. Pautler all declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Canadian Cancer Society's Steering Committee on Cancer Statistics: Canadian Cancer Statistics (2012). http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2012–English.pdf. Accessed October 29, 2013.
2. Witjes JA. Management of BCG failures in superficial bladder cancer: a review. *Eur Urol* 2006;49:790-7. http://dx.doi.org/10.1016/j.eururo.2006.01.017
3. Zlotta AR, Fleshner NE, Jewett MA. The management of BCG failure in non-muscle-invasive bladder cancer: an update. *Can Urol Assoc J* 2009;3:S199-205.
4. Kavoussi LR, Brown EJ, Ritchey JK, et al. Fibronectin-mediated Calmette-Guerin bacillus attachment to murine bladder mucosa. Requirement for the expression of an antitumor response. *J Clin Invest* 1990;85:62-7. http://dx.doi.org/10.1172/JCI114434
5. Ratliff TL, Palmer JO, McGarr JA, et al. Intravesical Bacillus Calmette-Guerin therapy for murine bladder tumors: initiation of the response by fibronectin-mediated attachment of Bacillus Calmette-Guerin. *Cancer Res* 1987;47:1762-6.
6. Hudson MA, Brown EJ, Ritchey JK, et al. Modulation of fibronectin-mediated Bacillus Calmette-Guerin attachment to murine bladder mucosa by drugs influencing the coagulation pathways. *Cancer Res* 1991;51:3726-32.
7. Shen ZJ, Wang Y, Ding GQ, et al. Study on enhancement of fibronectin-mediated bacillus Calmette-Guerin attachment to urinary bladder wall in rabbits. *World J Urol* 2007;25:525-9. http://dx.doi.org/10.1007/s00345-007-0198-z
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12. http://dx.doi.org/10.1016/j.jclinepi.2009.06.005
9. Yuge K, Kikuchi E, Tanaka N, et al. Clinical impact of anti-platelet medication in patients with non-muscle invasive bladder cancer treated with BCG therapy. *Urology* 2012;80:S218.
10. Boorjian SA, Berglund RK, Maschino AC, et al. Fibrin clot inhibitor medication and efficacy of bacillus Calmette-Guerin for bladder urothelial cancer. *J Urol* 2009;182:1306-12. http://dx.doi.org/10.1016/j.juro.2009.06.026
11. Gee JR, Jarrard DF, Bruskewitz RC, et al. Reduced bladder cancer recurrence rate with cardioprotective aspirin after intravesical bacille Calmette-Guerin. *BJU Int* 2009;103:736-9. http://dx.doi.org/10.1111/j.1464-410X.2008.08123.x
12. Heiner JG, Terris MK. Effect of advanced age on the development of complications from intravesical bacillus Calmette-Guerin therapy. *Urol Oncol* 2008;26:137-40. http://dx.doi.org/10.1016/j.urolonc.2007.04.005
13. Hudson MA, Yuan JJ, Catalona WJ, et al. Adverse impact of fibrin clot inhibitors on intravesical bacillus Calmette-Guerin therapy for superficial bladder tumors. *J Urol* 1990;144:1362-4.
14. Rogerson JW. Intravesical bacille Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder. *Br J Urol* 1994;73:655-8.
15. P'Ng K B, Walsh MD, Seymour GJ, et al. The adverse effect of fibrin-clot inhibiting drugs on intravesical bacillus Calmette-Guerin efficacy for superficial bladder cancer. *Aust N Z J Surg* 1993;63:127-30.
16. Witjes JA, vd Meijden AP, Doesburg W, et al. Influence of fibrin clot inhibitors on the efficacy of intravesical Bacillus Calmette-Guerin in the treatment of superficial bladder cancer. The Dutch Southeast Cooperative Urological Group. *Eur Urol* 1993;23:366-70.
17. Zuiverloon TC, Nieuweboer AJ, Vekony H, et al. Markers predicting response to bacillus Calmette-Guerin immunotherapy in high-risk bladder cancer patients: a systematic review. *Eur Urol* 2012;61:128-45. http://dx.doi.org/10.1016/j.eururo.2011.09.026
18. Alexandroff AB, Jackson AM, O'Donnell MA, et al. BCG immunotherapy of bladder cancer: 20 years on. *Lancet* 1999;353:1689-94. http://dx.doi.org/10.1016/S0140-6736(98)07422-4
19. Hudson MA, Ritchey JK, Catalona WJ, et al. Comparison of the fibronectin-binding ability and antitumor efficacy of various mycobacteria. *Cancer Res* 1990;50:3843-7.
20. Pan CW, Shen ZJ, Ding GQ. The effect of intravesical instillation of antifibrinolytic agents on bacillus Calmette-Guerin treatment of superficial bladder cancer: a pilot study. *J Urol* 2008;179:1307-11. http://dx.doi.org/10.1016/j.juro.2007.11.045
21. Jaeger TF. Categorical Data Analysis: Away from ANOVAs (transformation or not) and towards Logit Mixed Models. *J Mem Lang* 2008;59:434-46. http://dx.doi.org/10.1016/j.jml.2007.11.007
22. See WA, Chapman PH. Heparin prevention of tumor cell adherence and implantation on injured urothelial surfaces. *J Urol* 1987;138:182-6.
23. See WA, Miller JS, Williams RD. Pathophysiology of transitional tumor cell adherence to sites of urothelial injury in rats: mechanisms mediating intravesical recurrence due to implantation. *Cancer Res* 1989;49:5414-8.
24. Mohammed SI, Knapp DW, Bostwick DG, et al. Expression of cyclooxygenase-2 (COX-2) in human invasive transitional cell carcinoma (TCC) of the urinary bladder. *Cancer Res* 1999;59:5647-50.
25. Dovedi SJ, Kirby JA, Atkins H, et al. Cyclooxygenase-2 inhibition: a potential mechanism for increasing the efficacy of bacillus calmette-guerin immunotherapy for bladder cancer. *J Urol* 2005;174:332-7. http://dx.doi.org/10.1097/01.ju.0000161589.85869.ae

Correspondence: Dr. Stephen E. Pautler, Associate Professor, Divisions of Urology & Surgical Oncology, Departments of Surgery & Oncology, Schulich School of Medicine & Dentistry, Western University, South West Surgical Oncology Lead, Cancer Care Ontario, Urology, St. Joseph's Hospital, 268 Grosvenor St., London, ON N6A 4V2; fax: 519 646 6037; stephen.pautler@sjhc.london.on.ca