The value of a comprehensive primary outcome – results of a negative randomized control trial in the non-muscle invasive bladder cancer population

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Introduction: *American Urological Association (AUA) guidelines recommend intravesical chemotherapy to be given following transurethral resection of a bladder tumor. Prior studies have shown the benefit of mitomycin as well as gemcitabine. However, no study has compared the two agents.*

Materials and methods: *The study was designed as an open label 1:1:1 randomized controlled trial, comparing intravesical mitomycin, gemcitabine and saline as a single intraoperative instillation immediately following transurethral resection of suspected bladder tumor. Primary endpoint was any grade ≥ 3 events according to NCI CTCAE Version 4.03, this captures any return trip to the operating room for recurrence of cancer or other event (benign bladder/urethra). Secondary endpoints were progression free survival for urothelial cell carcinoma and adverse events.*

Results: *A total of 82 patients were enrolled and randomized, unfortunately the trial was suspended early due to protocol deviations. In an intention to treat analysis, freedom from grade > 3 events at 2 years was 74.8% in the no treatment arm, 51.0% in the mitomycin arm, and 56.0% in the gemcitabine arm ($p = 0.81$). Freedom from cancer recurrence for all patients was 62.3%. In the no treatment arm, it was 78.8%, and 50.7% and 63.6% in the mitomycin arm and gemcitabine arm respectively ($p = 0.28$). In a univariate analysis, the only patient variable significantly associated with the primary outcome was pathologic T stage ($p < 0.002$).*

Conclusion: *This study provides an example of a novel, patient centered primary outcome with the goal of determining which treatment paradigms provide the greatest oncologic and clinic benefit.*

Key Words: bladder cancer, transurethral resection, mitomycin, gemcitabine, randomized clinical trial

Introduction

Bladder cancer is very common worldwide, and approximately 70% are non-muscle invasive at presentation.[1] The standard for non-muscle invasive bladder cancer (NMIBC) treatment remains transurethral resection of a bladder tumor (TURBT) and intravesical therapy with either immune or chemotherapeutic agents.[2,3] Numerous studies have shown reduced recurrence[4] with instillation of intravesical chemotherapy immediately after TURBT. This is the standard of care according to EAU/AUA/SUO guidelines.[2,3] Despite its known benefits and recommendation, utilization of perioperative chemotherapy has been shown to be as low as 3.2% across the U.S. and Europe.[5]

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There is no recommendation in the guidelines on which intravesical agent to use in the perioperative setting. Historically, mitomycin has been used and a systematic review and meta-analysis of multiple studies has shown its efficacy in preventing recurrence versus resection alone (RR: 0.68, 95% CI:0.55-0.83).[4] Recently, the SWOG S0337 study[6] showed the efficacy of perioperative gemcitabine in preventing recurrence versus resection alone (HR: 0.66, 95% 0.48-0.90).[6] In a setting where two agents are comparable in oncologic outcomes it is beholden on the surgeon to determine which agent to use. Evidence comparing these two agents with regard to side effects is limited.[4] One study comparing mitomycin and gemcitabine in maintenance therapy for NMIBC showed a significantly lower number of adverse events ($p = 0.021$) in the gemcitabine group.[7] However, no study exists directly comparing the two agents immediately following TURBT. The goal of this study was to examine the differences between mitomycin and gemcitabine immediately following TURBT, while using a novel primary endpoint that the authors of this study feel provides a more patient centered outcome.

Materials and methods

This study was designed as a single institution open label, three-arm, randomized controlled trial (RCT). Its goal was to compare intravesical mitomycin C (40 mg in 40 mL normal saline) versus gemcitabine (2 grams in 100 mL normal saline) versus no adjuvant treatment as a single intraoperative instillation immediately following TURBT for suspected NMIBC. IRB approval was obtained from the Spectrum Health Institutional Review Board, SH-IRB#2016-030.

This study had two hypotheses. The first was that oncologic results would be equivalent across the TURBT/mitomycin and TURBT/gemcitabine arms, and both be significantly better than TURBT alone. The second hypothesis was that there would be more interventions for bladder stones in the TURBT/mitomycin arm compared with the TURBT/gemcitabine and TURBT alone arms. Therefore, we designed the primary outcome to account for both of these effects, selecting grade ≥ 3 events according to NCI CTCAE Version 4.03.[8] Briefly, this endpoint captures any return trip to the operating room (OR) for recurrence of cancer or other event, including removal of bladder stones, treatment for urinary stricture, etc. Secondary outcomes were the incidence of and time to first bladder cancer recurrence and the incidence of and time to dystrophic calcifications. The study was powered to detect a 25% difference in the primary objective: 300 patients, 100 in each arm. Accrual began May 6, 2016; however, enrollment was suspended on September 13, 2018 due to protocol deviations concerning randomization and physician bias, in the setting of limited funding and research staff expertise. All statistical analysis was performed with SAS v9.1.

Results

In response to an institutional call for investigator-initiated research protocols, we obtained a Cancer Program Internal Grant Initiative sponsored award for a trial evaluating intravesical treatment options after TURBT. We conducted patient interviews with current bladder cancer patients during preparation of the grant to determine the outcomes of greatest interest. We found that patients were most affected by returns to the operating room, and felt that office biopsy/fulguration was of similar impact as their routine cystoscopies. In particular, there was a subset of patients significantly bothered by recurrent stones that they experienced only following intravesical treatment as they had no prior history of urinary stone disease. Based on this information, we conducted a focus group with the Patient Family Advisory Committee members of our cancer center to review our trial design for the CPIGI award. Following this process, we adopted a novel primary endpoint: occurrence of any grade ≥ 3 event after treatment.

Following trial initiation, a total of 82 patients were randomized, 29 to mitomycin, 26 to gemcitabine, and 27 to no treatment. There were no statistical differences amongst the demographics of each arm, Table 1. Sixty-two patients were found to have NMIBC; 28 with low grade Ta, 23 with high grade Ta, and 11 with high grade T1 and/or carcinoma in situ (CIS); 20 patients were considered non-index, including 9 with muscle-invasive bladder cancer, 10 with benign tumors, and 1 with metastatic adenocarcinoma. Median follow up was 2.1 years (IQR: 1.5, 2.6).

Cancer recurrence was suspected in 41 patients (50%), with 34 patients going to surgery for this reason and 31 patients having pathologic evidence of cancer recurrence. A total of 17 office cystoscopies with bladder biopsy and/or fulguration were performed in study patients. The total number of patients experiencing grade ≥ 3 events was 44 (53.6%), which included 63 returns to the operating room (range: 1-8 per patient), 51 for suspected recurrence and 14 for bladder stones. One patient experienced a grade 4 event, a cardiac arrest 2 months after TURBT and after five of six planned induction BCG treatments, he died 7 months later.

TABLE 1. **Clinical characteristics and operative parameters of patients enrolled in the BIC study**

	All patients (n = 82)	No treatment (n = 27)	Mitomycin (n = 29)	Gemcitabine (n = 26)	p[1]
Age, years	73 (64-81)	74 (62-81)	74 (66-80)	69 (61-81)	0.77
Male	67 (82%)	21 (78%)	24 (83%)	22 (85%)	0.80
Caucasian	77 (94%)	25 (93%)	28 (97%)	24 (92%)	0.53
Smoking status					0.87
Current smoker	19 (24%)	7 (26%)	5 (18%)	7 (28%)	
Former smoker	37 (46%)	12 (44%)	13 (46%)	12 (48%)	
Never smoker	24 (30%)	8 (30%)	10 (36%)	6 (24%)	
Prior bladder cancer	27 (34%)	9 (33%)	8 (29%)	10 (40%)	0.68
Operative time, min	22 (15-42)	24 (12-40)	22 (14-38)	21 (16-56)	0.51
Length of stay, hrs	5 (4-8)	5 (4-8)	5.5 (4-9)	5 (4-9)	0.72
Outpatient surgery	71 (87%)	23 (85%)	26 (90%)	22 (85%)	0.83
Pain score in PACU[2]	0 (0-0)	0 (0-0)	0 (0-3.5)	0 (0-0)	0.48
Tumor volume, cm^3	1.0 (0.04-4.8)	1.6 (0.03-5.0)	0.82 (0.03-5.3)	1.1 (0.15-5.1)	0.94
High-grade UC	43 (52%)	14 (52%)	15 (52%)	14 (54%)	0.98
Clinical stage					0.32
Ta	51 (72%)	15 (65%)	15 (65%)	21 (84%)	
T1/CIS	11 (15%)	5 (22%)	3 (13%)	3 (12%)	
T2	9 (13%)	3 (13%)	5 (22%)	1 (4%)	

Data are presented as n (%) or median (interquartile range).
[1]comparisons between the 3 groups were made by Wilcoxon tests for continuous data and Chi square tests for nominal data.
[2]determined by Likert scale with a range of 1-10. Data were not available for 9 subjects.

TABLE 2. **Clinical outcomes**

	All patients (n = 82)	No treatment (n = 27)	Mitomycin (n = 29)	Gemcitabine (n = 26)	p[1]
Primary outcome					
Freedom from grade ≥ 3 event event[1,2]	59.8%	74.8%	51.0%	56.0%	0.81
Secondary outcomes					
Freedom from cancer recurrence[1]	62.3%	78.8%	50.7%	63.6%	0.28
Freedom from bladder stones/ dystrophic calcification[1]	55.7%	65.3%	50.4%	50.3%	0.69
Readmission after surgery	3 (3.7%)	1 (3.7%)	1 (3.6%)	1 (3.8%)	0.99

[1]kaplan-meier estimates at 2 years
[2]in brief, the NCI CTCAE Version 4.03 grades adverse events as follows: grade 3 include severe but non-life-threatening consequences that result in hospitalization and/or interventions, including elective radiologic or operative interventions; grade 4 events include life-threatening consequences, such as those requiring urgent reoperation; and grade 5 events result in treatment-related death.[7]

TABLE 3. **Predictors of grade ≥ 3 events after TURBT**

	Rate of grade ≥ 3	p[1]	Median time to event, months	p[1]
Gender		0.94		0.19
Male	52.2% (35/67)		20.4 (4.8, 27.1)	
Female	53.3% (8/15)		6.8 (4.4, 17.4)	
Smoking status		0.19		0.84
Current	52.4% (11/21)		18.0 (4.9, 21.2)	
Former	56.8% (21/37)		20.8 (4.0,28.3)	
Never	33.3% 8/24)		20.6 (4.8, 26.4)	
Prior bladder cancer history		1.0		0.004
Yes	51.9% (29/43)		25.1 (18.6, 31.7)	
No	51.9% (13/28)		6.9 (4.5, 23.4)	
Intravesical therapy		0.55		0.14
Gemcitabine	53.8% (14/26)		20.6 (4.9, 25.7)	
Mitomycin	44.8% (13/29)		6.8 (4.0, 21.1)	
None	59.3% (16/27)		21.5 (10.8, 31.9)	
Grade of urothelial carcinoma		0.078		0.41
High	67.4% (29/43)		20.4 (4.6, 27.5)	
Low	46.4% (13/28)		13.9 (5.3, 25.9)	
Pathologic stage		0.042		0.001
T2	100% (9/9)		3.5 (2.6, 4.4)	
T1/CIS	81.8% (9/11)		21.3 (18.3, 30.1)	
Ta	47.1% (24/51)		21.2 (6.9, 27.5)	

Data are presented as % () and median (interquartile range).
[1]comparisons were made by Chi square tests for nominal data and Wilcoxon tests for continuous data

In an intention to treat analysis, freedom from grade ≥ 3 events at 2 years was 74.8% in the no treatment arm, 51.0% in the mitomycin arm, and 56.0% in the gemcitabine arm (p = 0.81), Table 2. Freedom from cancer recurrence for all patients was 62.3%. In the no treatment arm, it was 78.8%, in the mitomycin arm it was 50.7% and 63.6% in the gemcitabine arm (p = 0.28). Freedom from bladder stones or dystrophic calcifications for all patients was 55.7%, with the no treatment arm 65.3%, mitomycin arm 50.4%, and gemcitabine arm 50.3% (p = 0.69).

We next sought to identify predictors of grade ≥ 3 events and time to grade ≥ 3 events, Table 3. The only predictor of grade ≥ 3 events was pathologic stage (p = 0.042). Median time to event was less in patients with no prior history of bladder cancer (p = 0.004). Time to event was significantly shorter in patients with pathologic T2 bladder cancer (p = 0.001), with all 9 patients undergoing subsequent treatment at median of 3.5 months after TURBT. Median time to grade ≥ 3 event was 21.3 months for T1/CIS and 21.2 months for Ta tumors. High grade T1 and CIS patients had greater number of events (HR:1.66, IQR:0.83, 2.51) when compared to Ta patients.

Discussion

This randomized clinical trial of gemcitabine versus mitomycin versus no treatment following TURBT ended without conclusive results. The hypothesis that perioperative chemotherapy would reduce the number of cancer recurrences was not supported by the data collected. We did, however, observe the variety of pathologic and clinical outcomes that affect quality-of-life in NMIBC patients. Of note, 43 patients went to the operating room following TURBT, including 9 solely for bladder stones likely related to intravesical treatment. In addition, although cancer recurrence was suspected in 41 patients, pathologic confirmation occurred in only 31 (76%). Office biopsy and fulguration was relatively common as well.

The aim of the trial was to provide patient-centered outcomes regarding which form of chemotherapy to use immediately following TURBT. During trial conception, we considered the input of bladder cancer patients and patient advisors and determined that evaluating returns to the OR (and more serious events) was the most important patient-centered endpoint.

Suspected tumor recurrence leading to operative cystoscopy is the main event to avoid, but occasionally these operative procedures are performed without finding pathologic tumor recurrence due to the findings of dystrophic calcifications or bladder stones. In discussion with our PFAC, the small tumor recurrences managed in the office had little impact on patient perception and quality of life. It is the opinion of the authors that, that these small recurrences have little impact on cancer progression and are less clinically relevant than a return trip to the OR. However, in any study comparing intravesical chemotherapy this outcome must be measured.

The oncologic outcomes of this study highlight the importance of a well powered study. Mitomycin has long been studied as an agent in treating superficial bladder cancer and preventing recurrence when given immediately following TURBT.[2-4] The recent SWOG study showed the clinical benefit of gemcitabine.[6] This study surprisingly had a higher recurrence rate in the arms with treatment, but this again highlights the impact of a drastically under powered study.

The most recent AUA guidelines, state that low- and intermediate-risk patients benefit the most from the immediate instillation of chemotherapy in preventing tumor recurrence.[3] These are the patients that have a lesser likelihood of cancer recurrence and progression. As such, they have a less strenuous follow up plan and often require less treatment overall for their disease. Thus, the impact of this novel primary outcome becomes even more relevant, as reductions in the number of procedures for non-cancer related concerns (bladder stones, dystrophic calcifications) will have an even larger impact on quality of life in these patients.

In an era where increasing focus is being placed on cost containment without sacrificing quality, this represents a unique model moving forward for future trials. For patients with NMIBC, a primary outcome of grade ≥ 3 events give a pragmatic answer to important clinical problems currently unaddressed. We hope this study encourages further research to determine which treatment paradigms provide the greatest oncologic and clinical benefit in conjunction with high-quality TURBT for NMIBC.

The limitations of this study are evident given the early closure and being underpowered. Enrollment was suspended due to protocol deviations concerning randomization and physician bias. Crossover occurred after randomization in only four (4.8%) patients. A review of the protocol deviations revealed the primary errors made were noted during the consent process. Specifically, patients were consented by individuals not identified as part of the research team and others consented the day of the procedure, both in violation of the protocol. Despite these protocol deviations, we consider this study relevant to the literature given its novel design.

Conclusion

This RCT intended to demonstrate whether TURBT with perioperative gemcitabine or mitomycin or no chemotherapy led to fewer grade ≥3 events, which include any operative interventions for cancer or other indications. The hypothesis was unable to be answered due to the early closure of the study. Future trials should strongly consider this primary outcome to determine which treatment paradigms provide the greatest oncologic and clinical benefit to patients with NMIBC.

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