Intravesical bacillus Calmette-Guérin versus chemohyperthermia for high-risk non-muscle-invasive bladder cancer

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Abstract

Introduction: Patients with high-risk non-muscle invasive bladder cancer (NMIBC) need adjuvant intravesical treatment after surgery. Although bacillus Calmette-Guérin (BCG) is highly effective, new adjuvant treatments to decrease recurrences and toxicity have been studies. We performed a retrospective propensity score-matched study to compare the efficacy of BCG and chemohyperthermia (C-HT).

Methods: We included 1937 patients diagnosed with bladder cancer between January 2004 and January 2014. The primary efficacy endpoint was recurrence-free interval. Patients treated with C-HT were matched with patients treated with BCG using propensity score-matched analysis. Cox-regression models were used to estimate the association between intravesical treatments and the presence of recurrence and progression.

Results: Of the 710 patients treated with intravesical treatments, 40 and 142 were eligible for inclusion in C-HT and BCG groups, respectively. Following case matching, there were no differences in patient or tumour characteristics between treatment groups. The 2-year recurrence-free interval in C-HT and BCG groups were 76.2% and 93.9%, respectively ($p = 0.020$). C-HT treatment (hazard ratio [HR] 5.42; 95% confidence interval [CI] 1.11–26.43; $p = 0.036$) and high-grade tumour (HR 4.60; 95% CI 1.01–20.88; $p = 0.048$) are associated with an elevated odds of tumour recurrence. In multivariate Cox-regression analysis, there was no significant difference between C-HT and BCG in the odds of recurrence ($p = 0.054$). There were no differences in progression between C-HT and BCG.

Conclusion: C-HT is not as effective treatment as BCG in high-risk NMIBC patients who are BCG-naive. Although, there were no significant difference in the odds of recurrence, recurrence-free interval is significantly improved by the administration of BCG.

Introduction

Bladder cancer is the fourth most common cancer in American men and, at diagnosis, more than 75% of these cancers are non-muscle-invasive (NMIBC).[1] Although the 5-year survival for NMIBC is more than 90%, the survival period is not disease-free.[2,3] After the initial transurethral resection (TUR), about half of NMIBC patients are at risk for disease recurrence and, to lesser extent, progression to muscle-invasive disease.[1,3] To reduce recurrence and progression, adjuvant intravesical therapy is given and recommended by European Association of Urology (EAU) guidelines.[3]

Instillation of bacillus Calmette-Guérin (BCG) is considered more effective than chemotherapy for NMIBC, representing the first-line option in high-risk patients.[3,4] BCG and intravesical chemotherapy are acceptable alternatives for intermediate-risk patients.[3,4] Although BCG has demonstrated superiority than chemotherapy, it needs to be balanced with side effects.[5] Due to side effects and failure of BCG, new chemotherapy agents and device-assisted instillation have been tested in high-risk patients.[6]

Intravesical mitomycin-C (MMC) for NMIBC has been widely studied.[4] Several studies have demonstrated the benefit of chemohyperthermia (C-HT) over intravesical chemotherapy alone.[6] To enhance the efficacy of MMC, two different methods for intravesical C-HT delivering have been introduced: microwave-induced heating (Synergo, Medical Enterprises, Amsterdam, Netherlands) and conductive heat (UniThermia, Elmedical, Hod-Hasharon, Israel).[7] Although studies have promising results of C-HT in high-risk NMIBC, to our knowledge, there are no comparative studies on the effectiveness of BCG and C-HT. In this retrospective study, we evaluated recurrence-free interval between BCG and C-HT, using propensity score-matched analysis.

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Methods

Patient selection and study design

We included 1937 patients who underwent TUR for bladder cancer between January 2004 and January 2014 in this prospectively collected database. Patients with high-risk of NMIBC treated with intravesical C-HT or BCG instillation, and patients who performed second-TUR were included.[3,8] We excluded patients treated with reduced dose of BCG, those with <1 cm diverticulum in the bladder, those with histopathology non-urothelial carcinoma, those with concomitant urothealial carcinoma in the urethra or upper urinary tract, those with low bladder capacity (<150 mL), and those with high post-voided residual urine (>100 mL). A control group of patients on BCG who met the inclusion/exclusion criteria were selected from the patients in the database.

C-HT was performed with a bladder wall thermochemotherapy (BWT, Elmedical, Hod-Hasharon, Israel) unit and an 18-French flexible UniThermia catheter. Each session consisted of 40 mg MMC in 50 mL saline solution and bladder wall hyperthermia to 42.5 to 45°C for 60 minutes. Induction of C-HT and MMC combination therapy was administered weekly for 6 consecutive weeks; there were also 3 weekly instillations at month 3 and month 6. BCG was instilled weekly for 6 consecutive weeks. The choice of maintenance was determined by the physician and/or patient.

Cystoscopy and urine cytology were repeated every 3 months during the first 2 years, every 6 months between the third and fifth year, and annually in the subsequent years. All visible lesions were resected with recurrence determined by histological confirmation. Intravenous urography and computed tomography urography were performed annually to evaluate upper urinary tract.

Outcome definition

Recurrence-free interval and the presence of recurrence and progression were evaluated. Recurrence-free interval was measured from the first intravesical treatment to the first recurrence, including progression to muscle-invasive disease, distant metastases, and death due to bladder cancer. Secondary end points included the progression-free interval (muscle-invasive disease, distant metastases, death due to bladder cancer).

Propensity score matching and statistical analysis

Patients treated C-HT were matched to patients treated BCG using propensity score-matched analyses. The propensity score were calculated for each patient using multivariable logistic regression model based on tumour T-stage, grade, multiplicity, diameter, patient age, and gender. Based on the resulting propensity score, a case was matched to a control case using a caliper of 0.01. Matching for the propensity score was performed using the R 3.1.0 (http://www.r-project.org/).

We compared parametric variables using t-tests and categorical variables using the chi-square test. Following case matching, we evaluated the unadjusted differences between treatment groups using the McNemar test. The duration of survival curves was estimated using the Kaplan-Meier technique to estimate the probability of local recurrence. The association between time and recurrence/progression was compared using backward stepwise Cox regression model. Tests were 2-sided and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 19.0 for Windows. The study was approved by our institutional ethics committee.

Results

Between January 2004 and January 2014, 710 patients were treated by intravesical treatments at our institution and were assessed for eligibility (Fig. 1). In total, there were 182 patients in our study population: 40 in the C-HT group and 142 in the BCG group, after applying inclusion and exclusion criteria. We tallied their baseline patient and tumour characteristics (Table 1).

Before case matching, we found that the C-HT treatment group was older and there were no significant differences in other variables (Table 1). Following case matching, there were no differences in any patient or tumour characteristics between treatment groups (Table 2). The overall median follow-up was 33 (interquartile range [IQR): 24–39) months. The C-HT and BCG treatment groups were followed for a median duration of 33 (IQR: 21–36) and 33 (IQR: 28–66) months, respectively.

Using the McNemar test, recurrence developed in 14/39 (35.9%) and 8/39 (20.5%) patients in the C-HT and BCG groups ($p < 0.05$). The 1-year recurrence-free interval was 82.1% and 97.4%, the 2-year recurrence-free interval was 70.1% and 89.5% in C-HT and BCG groups, respectively ($p = 0.006$) (Fig. 2, part A). In the univariate Cox regression analysis, tumour recurrence was associated with tumour grade (odds ratio [OR] 4.60, 95% CI 1.01–20.88) and intravesical treatment (OR 4.18, 95% CI 1.37–12.71) (Table 3). In the multivariate Cox regression analysis, tumour grade and intravesical treatment were not associated with tumour recurrence.

Using the McNemar test, progression developed in 6/39 (15.4%) and 3/39 (7.7%) patients in C-HT and BCG groups ($p < 0.05$). The 1-year progression-free interval was 89.7% and 97.4%, the 2-year progression-free interval was 87.2% and 94.9% in C-HT and BCG groups, respectively ($p = 0.124$)

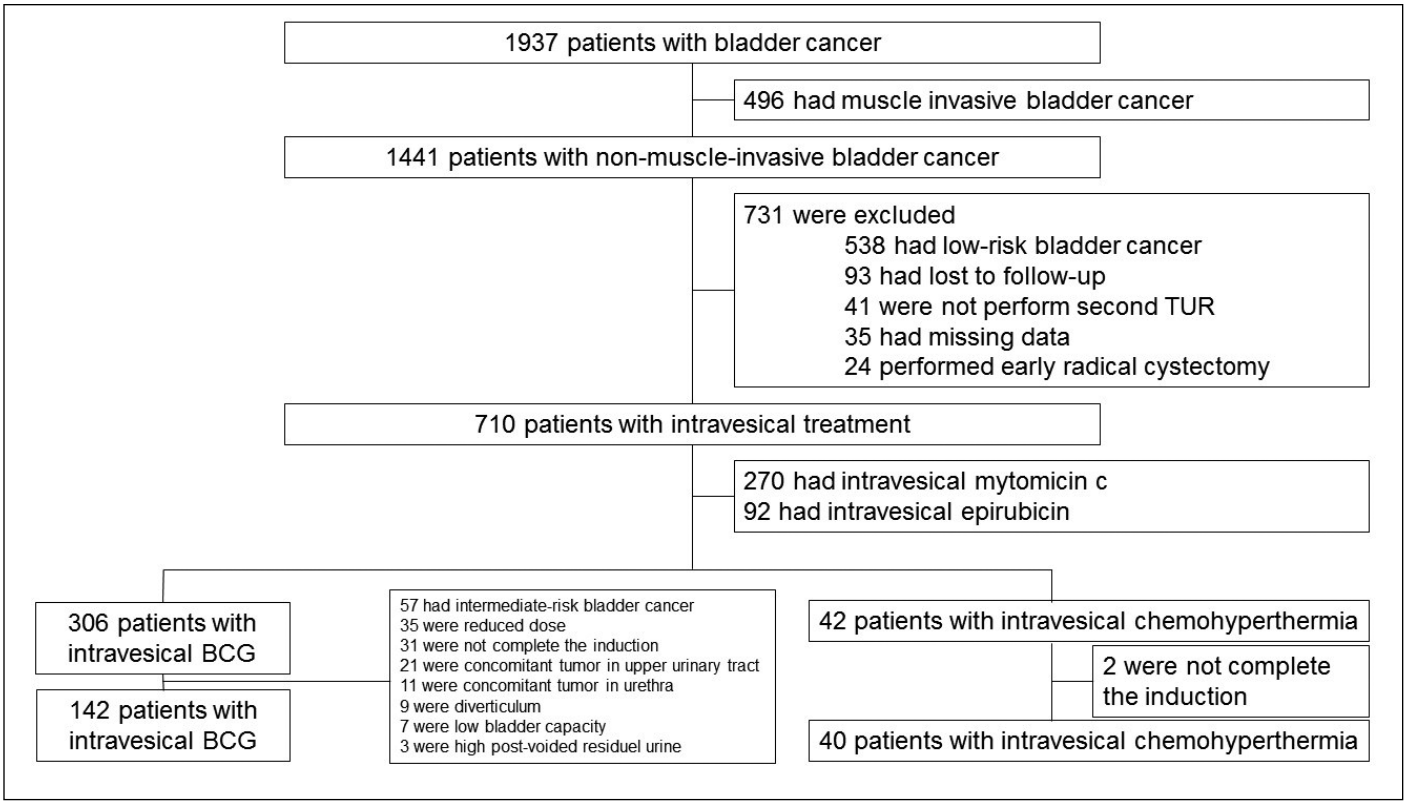

Fig. 1. Bladder cancer cohort flowchart. TUR: transurethral resection; BCG: bacillus Calmette-Guérin.

Table 1. Patient and tumour characteristics by treatment group

	Overall		C-HT		BCG		*p* value
No. patients	182		40		142		—
Mean ± SD age (range)	64.95 ± 10.45 (30–86)		68.26 ± 9.26 (47–84)		64.02 ± 10.61 (30–86)		0.023
Gender (%)							
Male	167	(91.8)	38	(95.0)	129	(90.8)	0.528
Female	15	(8.2)	2	(5.0)	13	(9.2)	
Presentation (%)							
Primary	118	(64.8)	27	(67.5)	91	(64.1)	0.689
Recurrent	64	(35.2)	13	(32.5)	51	(35.9)	
Tumour size (%)							
Less than 3 cm	73	(40.1)	14	(35.0)	59	(41.5)	0.455
3 cm or greater	109	(59.9)	26	(65.0)	83	(58.5)	
Tumours (%)							
Single	71	(39.0)	13	(32.5)	58	(40.8)	0.339
Multiple	111	(61.0)	27	(67.5)	84	(59.2)	
Stage (%)							
Ta	45	(24.7)	10	(25.0)	35	(24.6)	0.988
T1	127	(69.8)	28	(70.0)	99	(69.7)	
CIS	10	(5.5)	2	(5.0)	8	(5.6)	
Grade (%)							
Low	65	(35.7)	16	(40.0)	49	(34.5)	0.522
High	117	(64.3)	24	(60.0)	93	(65.5)	
Concomitant CIS (%)							
Yes	33	(18.1)	8	(20.0)	25	(17.6)	0.728
No	149	(81.9)	32	(80.0)	117	(82.4)	

BCG: bacillus Calmette-Guérin; C-HT: chemohyperthermia; CIS: carcinoma in situ; SD: standard deviation.

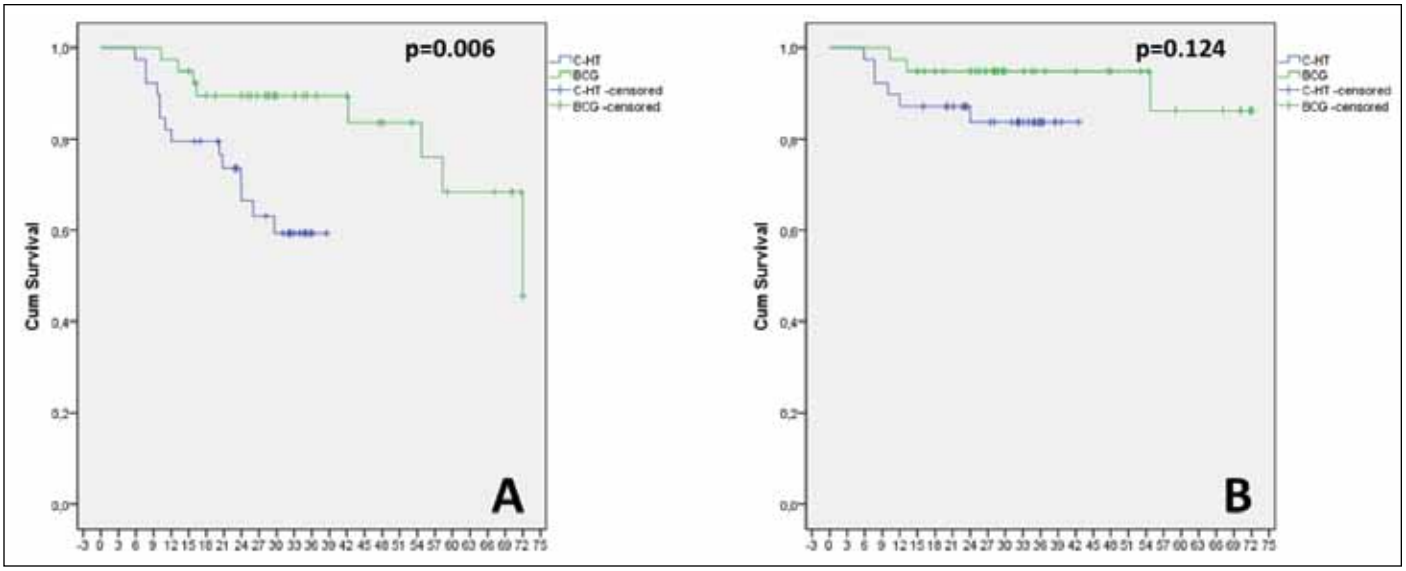

Fig. 2. Kaplan-Meier curve, stratified by intravesical chemohyperthermia (C-HT) and bacillus Calmette-Guérin (BCG) treatments. A. Recurrence-free survival. B. Progression-free survival.

(Fig. 2, part B). There were no associations between progression and age, gender, tumour size, multiplicity, stage, grade, concomitant carcinima in situ (CIS), and intravesical treatment in univariate Cox regression analysis (Table 3).

Discussion

We evaluated treatment efficacy between intravesical C-HT and BCG instillation in this retrospective cohort study. In

Table 2. Patient and tumour characteristics of 78 case matched pairs

	Overall		C-HT		BCG		*p* value
No. patients	78		39		39		—
Mean ± SD age (range)	68.04 ± 8.81 (47–84)		68.05 ± 9.29 (47–84)		68.02 ± 8.42 (48–82)		0.990
Gender (%)							
Male	73	(93.6)	37	(94.9)	36	(92.3)	α
Female	5	(6.4)	2	(5.1)	3	(7.7)	
Presentation (%)							
Primary	52	(66.7)	26	(66.7)	26	(66.7)	0.053
Recurrent	26	(33.3)	13	(33.3)	13	(33.3)	
Tumour size (%)							
Less than 3 cm	29	(37.2)	14	(35.9)	15	(38.5)	0.154
3 cm or greater	49	(62.8)	25	(64.1)	24	(61.5)	
Tumours (%)							
Single	26	(33.3)	13	(33.3)	13	(33.3)	0.053
Multiple	52	(66.7)	26	(66.7)	26	(66.7)	
Stage (%)							
Ta	17	(21.8)	10	(25.6)	7	(17.9)	α
T1	57	(73.1)	27	(69.2)	30	(76.9)	
CIS	4	(5.1)	2	(5.1)	2	(5.1)	
Grade (%)							
Low	33	(42.3)	15	(38.5)	18	(46.2)	0.441
High	45	(57.7)	24	(61.5)	21	(53.8)	
Concomitant CIS (%)							
Yes	13	(16.7)	8	(20.5)	5	(12.8)	<0.05
No	65	(83.3)	31	(79.5)	34	(87.2)	
Tumour recurrence (%)							
Yes	22	(28.2)	14	(35.9)	8	(20.5)	<0.05
No	56	(71.8)	25	(64.1)	31	(79.5)	

α: at least one number too small for analysis; BCG: Bacillus Calmette-Guérin; C-HT: Chemohyperthermia; CIS: carcinoma in situ; SD: standard deviation.

Table 3. Univariable and multivariable Cox regression model predicting recurrence and progression in 78 case matched pairs

	Recurrence				Progression	
	Univariable		Multivariable		Univariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.01 (0.96–1.06)	0.678			1.02 (0.92–1.12)	0.640
Age (≥68.4 vs. <68.4)	1.12 (0.48–2.63)	0.788			2.13 (0.38–11.88)	0.386
Gender (male vs. female)	2.67 (0.77–9.24)	0.119			2.16 (0.19–14.44)	0.738
Presentation (recurrent vs. primary)	1.24 (0.51–3.01)	0.629			5.42 (0.94–31.31)	0.059
Tumour size (≥3 cm vs. <3 cm)	1.29 (0.52–3.20)	0.576			1.91 (0.38–9.47)	0.428
Tumours (multiple vs. single)	1.25 (0.49–3.22)	0.632			2.46 (0.28–21.33)	0.411
Stage						
(T1 vs. Ta)	1.35 (0.29–6.23)	0.582			1.24 (0.14–10.74)	0.842
(CIS vs. Ta)	α	α			α	α
(T1 and CIS vs. Ta)	1.37 (0.50–3.76)	0.535			1.13 (0.13–9.78)	0.908
(T1 vs. Ta and CIS)	1.09 (0.42–2.80)	0.847			1.71 (0.19–14.81)	0.623
Grade (high vs. low)	4.60 (1.01–20.88)	0.048	4.09 (0.89-18.70)	0.069	3.51 (0.41–30.09)	0.252
Concomitant CIS (yes vs. no)	1.46 (0.53–4.01)	0.458			2.46 (0.44–13.57)	0.300
Intravesical treatment (C-HT vs. BCG)	4.18 (1.37–12.71)	0.012	3.78 (0.96-10.52)	0.054	1.72 (0.28–10.36)	0.550

α: at least one number too small for analysis; HR: hazard ratio; BCG: bacillus Calmette-Guérin; C-HT: chemohyperthermia; CIS: carcinoma in situ; HR: hazard ratio; CI: confidence interval.

the univariate Cox-regression analysis, the odds of tumour recurrence was more than 4.18 times greater in the C-HT group compard with the BCG group; however, there was no significant difference between the treatment groups for the odds of progression. In the multivariate Cox-regression analysis, there was no significant difference between C-HT and BCG in the odds of recurrence ($p = 0.054$).

In high-risk NMIBC, the expected recurrence rate is 49% at 5 years.[9] The sources of recurrence are implantation during TUR, persisting CIS, and preclinical lesions.[3,10,11] In high-risk NMIBC, intravesical BCG is indicated.[3] Intravesical BCG prevents 31% to 50% of tumour recurrence, compared to TUR alone.[12] However, the side effects of BCG are remarkable, and the treatment discontinuation rate of BCG for toxicity is 7% to 19%.[13] In a meta-analysis, a 32% reduction in tumour recurrence for BCG maintenance compared to MMC was found.[4] MMC should be considered a less effective alternative treatment for patients intolerant to BCG.

BCG-failure and its side effects are undesirable. As a result, more effective and safe treatment options have been studied.[6] Even though new treatments have been reported, more results and larger studies are needed.[6,12,14-16] Colombo and colleagues found that C-HT is more effective than MMC alone.[17] The 10-year disease-free survival rate for C-HT and MMC alone were 53% and 15%, respectively.[17] Moskovitz and colleagues reported their 10-year experience of C-HT, in which their disease-free rate was 67.2% at 2 years and their tumour recurrence was 28%.[18] In a meta-analysis, the overall bladder preservation rate of 87.6% was found after C-HT.[6] In these published studies, the intravesical C-HT was performed by microwave-induced heating device (Synergo).[6,17,18] In our study, we performed intravesical C-HT with UniThermia, which is based on conductive heating. Although MMC stability and systemic absorption were comparable between conductive and microwave-induced heating, there are no studies evaluating the effectiveness of UniThermia.[7] The efficacy of the different heating methods may not be identical in tumour recurrence. Additionally, there are no studies comparing C-HT and BCG in NMIBC patients. To our knowledge, this is the first study comparing C-HT and BCG. Even though there were no significant differences in the odds of recurrence between C-HT and BCG in multivariate Cox-regression analysis, the reasons for this may include small sample size and overmatching.

Our study has its limitations. First, it was a retrospective cohort study with an inherent potential for bias, although we conducted the current study using propensity score-matched analyses. Second, a relatively small number of patients were enrolled in this study and the C-HT arm follow-up period was relatively short. Although our results need to be validated with prospective randomized trials, it is the first study in which C-HT is compared with BCG in NMIBC patients. Until these studies are performed, intravesical C-HT instillation is not a first treatment option in high-risk NMIBC.

Conclusion

Recurrence-free interval was significantly improved in NMIBC patients treated with intravesical BCG instillation, compared to patients treated with intravesical C-HT instillation. Although our study has several limitations, we suggest that intravesical BCG instillation remain the standard adjuvant treatment in high-risk NMIBC.

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