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A Phase I Trial of Intravesical Cabazitaxel, Gemcitabine and Cisplatin for the Treatment of Nonmuscle Invasive bacillus Calmette-Guérin Unresponsive or Recurrent/Relapsing Urothelial Carcinoma of the Bladder

Guarionex J. DeCastro^{*}, Wilson Sui, Jamie S. Pak, Shing M. Lee, Dara Holder, Max M. Kates, Renu K. Virk, Charles G. Drake, Christopher B. Anderson, Bridget James, Cory T. Abate-Shen, James M. McKiernan

Department of Urology (GJD, JSP, CBA, JMM), Department of Pathology and Cell Biology (RKV), Division of Hematology/Oncology (CGD), Herbert Irving Comprehensive Cancer Center (BJ), Irving Cancer Research Center (CTA-S), Columbia University Irving Medical Center, Department of Biostatistics (SML), Columbia University Mailman School of Public Health, New York, New York, Department of Urology (WS), Vanderbilt University Medical Center, Nashville, Tennessee, Department of Urology (DH), University of Wisconsin-Madison, Madison, Wisconsin, and James Buchanan Brady Urological Institute (MMK), Johns Hopkins School of Medicine, Baltimore, Maryland

Abstract

Purpose: For patients with bacillus Calmette-Guérin unresponsive or recurrent/relapsing nonmuscle invasive bladder cancer, multi-agent intravesical trials have been limited. In this study we investigate the safety of intravesical cabazitaxel, gemcitabine and cisplatin in the salvage setting.

Materials and Methods: This was a dose escalation, drug escalation trial for patients with bacillus Calmette-Guérin unresponsive or recurrent/relapsing nonmuscle invasive bladder cancer who declined or were ineligible for radical cystectomy. All patients underwent a 6-week induction regimen of sequentially administered cabazitaxel, gemcitabine and cisplatin. Complete response was defined as no cancer on post-induction transurethral bladder tumor resection and negative urine cytology, while partial response allowed for positive cytology. Responders continued with maintenance cabazitaxel and gemcitabine monthly for the first year and bimonthly for the second year.

Results: A total of 18 patients were enrolled. Mean age was 71 years, median followup was 27.8 months (range 16.3 to 46.9) and mean number of previous rounds of intravesical therapies before trial enrollment was 3.7. Nine patients (50%) had received intravesical chemotherapy after bacillus Calmette-Guérin and 7 (39%) were previously treated in a phase I clinical trial setting. At enrollment 6 (33%) subjects had T1 disease and 13 (72%) had carcinoma in situ. There were no dose limiting toxicities. Initial partial and complete response rates were 94% and 89%,

^{*}Correspondence: Department of Urology, Columbia University Irving Medical Center (gjd16@cumc.columbia.edu).

respectively. At 1 year recurrence-free survival was 0.83 (range 0.57 to 0.94) and at 2 years estimated recurrence-free survival was 0.64 (0.32 to 0.84).

Conclusions: In this high risk and highly pretreated cohort of bacillus Calmette-Guérin unresponsive or recurrent/relapsing nonmuscle invasive bladder cancer cases combination intravesical cabazitaxel, gemcitabine and cisplatin was a well tolerated and potentially effective regimen.

Keywords

urinary bladder neoplasms; administration; intravesical

Bladder cancer is the 11th most common solid organ malignancy worldwide, with more than 540,000 new cases diagnosed in 2018.¹ In the United States alone 81,190 patients will be diagnosed and 17,240 died of the disease in 2018.² For those with nonmuscle invasive bladder cancer with high risk features the use of a 6-week induction BCG course followed by maintenance has been shown to reduce the risk of disease recurrence by 30% to 40%, and is considered the standard of care.^{3–7} However, up to 40% of high risk cases treated with BCG will relapse and 20% will progress to muscle invasive disease within 5 years.⁸

Patients with BCG unresponsive NMIBC face a difficult choice between undergoing radical cystectomy or opting for salvage intravesical therapies. Although yielding a high rate of disease-free survival, radical cystectomy is associated with mortality rates ranging from 0.7% to 5.6% at high volume centers and complication rates as high as 60%.^{9,10}

Salvage intravesical treatments have been explored for more than 40 years but there has been little progress in terms of lasting efficacy. Only 1 intravesical treatment for BCG unresponsive disease has received FDA (U.S. Food and Drug Administration) approval, and it was valrubicin in 1997 under orphan drug status. Its approval was based on a nonrandomized phase II trial in patients with CIS-only disease that demonstrated a modest 21% recurrence-free survival at 6 months, decreasing to less than 10% at the end of the study.¹¹ Intravesical gemcitabine monotherapy has shown limited efficacy in this high risk group, with 1-year RFS of 28%.¹² Sequential use of salvage gemcitabine and docetaxel in a similar high risk group has shown improved but still modest results of 49% RFS at 1 year.¹³

In 2013 we conducted a preclinical trial using a genetically engineered mouse model with bladder specific combined loss of function of the *p53* and *Pten* tumor suppression genes to evaluate a combination of intravesical multidrug platinum based chemotherapy.¹⁴ Based on these results we designed and conducted the first phase I trial to explore the safety and toxicity of a novel combinatorial intravesical chemotherapeutic strategy consisting of cabazitaxel, gemcitabine and cisplatin in patients with high grade, BCG unresponsive or relapsing NMIBC.

MATERIALS AND METHODS

Subjects were required to be 18 years old or older, with an ECOG status of 0 or 1, and a histologically confirmed diagnosis of nonmuscle invasive T1, high grade Ta or CIS at the study institution. Involvement of the prostatic urethra with CIS and/or high grade

Ta/T1 disease was allowed, but patients with upper urinary tract disease were excluded from analysis. All patients were categorized as BCG unresponsive or recurrent/relapsing. BCG unresponsive disease was defined as biopsy proven recurrence within 6 months of receiving a 6-week induction course of BCG followed by at least 3 additional weekly maintenance treatments. BCG recurrent/relapsing disease was defined as reappearance of high risk disease after achieving a tumor-free status by 6 months following a full induction course of BCG with or without maintenance BCG. In the case of BCG relapsing disease, recurrence must have been documented within 18 months following the last dose of BCG.

Patients who received second line salvage therapies for BCG unresponsiveness after relapse and/or recurrence were eligible. All grossly visible disease was resected endoscopically before enrollment and pathological stage was confirmed at the study institution. Inclusion required that subjects either refuse or be deemed medically ineligible for radical cystectomy.

The study received institutional review board approval (IRB No. AAAM8506) and funding support by Sanofi Genzyme. Five intravesical dose combinations of gemcitabine, cabazitaxel and cisplatin were evaluated. In general, cabazitaxel was administered on Mondays, gemcitabine on Wednesdays and cisplatin every other Friday, with instructions to void after 1 to 2 hours. The dose of gemcitabine was held fixed at 2,000 mg/100 ml saline based on a previous study,¹² while adding or increasing doses for the 2 other agents (table 1). While cisplatin was dosed weekly in the original protocol it was modified to be dosed biweekly after the enrollment of the first patient to receive cisplatin due to concern for the development of hypersensitivity reaction.^{15,16}

Patients who achieved partial or complete response proceeded to maintenance therapy for a maximum of 2 years. The first 12 months included 1 monthly cycle of cabazitaxel and gemcitabine at previously established dosage (5 mg and 2,000 mg, respectively), and for the second 12 months treatments were administered bimonthly. Intravesical cisplatin was not used in the maintenance regimen. At the initial post-induction cystoscopy obligatory biopsies were performed of any suspicious areas as well as random biopsies throughout the bladder. Subsequent biopsies were performed only when clinically indicated.

Dose escalation and the estimation of the maximum tolerated dose were based on the 2-stage continual reassessment method.¹⁷ Dose limiting toxicity was defined as any nonhematologic grade 3 or 4 systemic or local toxicity at least possibly related to the study drug using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. In the first stage of the 2-stage continual reassessment method patients were assigned to cohorts of 2 patients starting from the lowest dose level as previously described.¹⁸ Once a DLT was observed, dose assignments were based on the continual reassessment method with a cohort of size 1. The dose toxicity model was calibrated such that the method would eventually select a dose that yielded between 20% and 30% DLT.^{19,20} The protocol was later modified to recruit 18 patients (10 patients at the highest dose level) given the absence of any DLT.

Assessment for adverse events was based on patient history at every treatment encounter as well as periodic laboratory testing. Assessment for response was based on cystoscopic

examination and urine cytology every 3 months throughout the maintenance period, and computerized tomography or magnetic resonance imaging performed at the 6th, 12th and 24th months. Initial complete response was defined as negative urine cytology and cystoscopic biopsy at 3 months following initial 6 weeks of treatment. Initial PR was defined as no evidence of disease on biopsy but positive cytology.

RESULTS

Table 2 details patient characteristics. Between December 2014 and November 2017, 18 patients were enrolled. Four (22%) were female, median age was 73 years (range 44 to 88) and median followup was 27.8 months (range 16.3 to 46.9). At the time of enrollment all patients had recurrence within 6 months after their last intravesical treatment. Six (33%) had recurrence with T1 disease, 13 (72%) with CIS and 3 (17%) with CIS or high grade papillary disease within the prostatic urethra only. The median number of previous rounds of intravesical therapies before enrollment was 3 (range 2 to 8) with 12 (67%) having received 3 or more therapies. This includes the 2 rounds of BCG required to be classified as BCG unresponsive or recurrent/relapsing. Appendix 1 details the exact nature of intravesical therapies received per patient before enrollment. Nine subjects (50%) had received intravesical chemotherapy before enrollment and 7 (39%) had been treated in a phase I clinical trial setting.

Table 3 details the frequency and severity of each reported AE. The most common complaints were urinary urgency and dysuria. Of the 18 subjects enrolled 12 (67%) reported at least 1 grade 1 or 2 AE. No patient experienced a DLT, so estimation of maximum tolerated dose was not possible. There were no AEs reported greater than grade 2, no evidence of systemic absorption by hematologic criteria and no episodes of cisplatin hypersensitivity reaction. The supplementary table (<https://www.jurology.com>) details AEs per treatment dose level.

Figure 1 is a Kaplan-Meier curve of RFS for all 18 subjects. Median followup was 27.8 months (range 16.3 to 46.9). Initial CR was observed in 16 of 18 (89%) patients, increasing to 17 of 18 (94%) if partial responders (ie negative biopsy but positive cytology) are included. The single biopsy proven failure within 3 months occurred in the prostatic urethra in a subject with high grade PU involvement at enrollment. At 12 months 2 additional patients had biopsy proven recurrence, 1 also within the prostatic urethra and another with CIS in the bladder, resulting in a 1-year RFS of 0.83 (range 0.57 to 0.94). Estimated RFS at 2 years was 0.64 (0.32 to 0.84). Since dosing of cisplatin and cabazitaxel was increased with subsequent cohorts only the last 10 (of 18) subjects received the highest dose (fig. 2). Median followup for this group dropped to 24.1 months (range 16.3 to 28.9) but CR at 3 months and 1-year RFS were both 100%. Estimated RFS at 2 years for this group was 0.83 (0.27 to 0.97). All recurrences were biopsy proven and there were no patients with radiologic evidence of progression before diagnosis based on biopsy.

Figure 3 details the clinical outcomes for each subject. Overall median time to recurrence was 27 months. Excluding patients with recurrence within the prostatic urethra only there was a single recurrence occurring at 10.4 months. At last followup 7 cases had recurred, 1

had hepatocellular carcinoma (and was censored), and 10 (56%) remained disease-free and are still being followed.

Cystectomy-free survival at 1 year was 0.94 (0.67 to 0.99) and at 2 years was estimated to be 0.81 (0.52 to 0.94). Of the 7 patients who had recurrence 5 have undergone radical cystectomy while 2 refused cystectomy (Appendix 2). Of the 5 cystectomy cases 3 had no residual carcinoma within the bladder, as 2 had prostatic urethral disease (with 1 N+) and 1 ureteral disease only (also N+). Of the remaining 2 cystectomy cases 1 had pT2N0 disease in the bladder and PU and 1 had pT4N2 disease (invasion into the prostatic glands/stroma).

DISCUSSION

Single agent systemic chemotherapies originally developed by Farber et al in the 1950s were historically unsuccessful in curing hematologic or solid malignancies. It was not until the introduction of platinum containing multidrug chemotherapy regimens in the 1970s that durable responses were seen in genitourinary malignancies.²¹ Studies by Yagoda and Sternberg in the 1980s in metastatic urothelial carcinoma eventually led to the development of combined methotrexate, vincristine, adriamycin and cisplatin in the treatment of urothelial carcinoma. During this evolution of systemic therapies the intravesical therapeutic paradigm has remained largely adherent to a single-drug, weekly regimen.²²

Several trials using single agent intravesical regimens have been used in BCG unresponsive and recurrent/relapsing cases. In our previous institutional study from 2003 to 2006, 18 patients underwent induction and/or maintenance with intravesical docetaxel.^{23,24} With a median followup of 13.3 months RFS at 1 and 2 years was 61% and 44%, respectively. Single agent gemcitabine given twice weekly has not yielded significantly better results, with a reported CR rate of 50%, and 2-year RFS of 6.7%.²⁵ In 2014 we reported on 28 patients with BCG unresponsive disease who underwent treatment with intravesical nanoparticle albumin bound paclitaxel.²⁶ Complete response after initial treatment was observed in 10 patients (29%) and this subset remained disease-free at 1 year.

There have been several multidrug intravesical regimens reported for salvage treatment.^{27–29} Lightfoot et al reported on a multi-institutional experience with 6 weekly treatments of sequential gemcitabine and mitomycin C.²⁸ RFS at 1 and 2 years was 48% and 38%, respectively, although notably 10 of the 52 patients in this study were BCG naïve and 6 had Ta LG disease only. A similar regimen of sequential gemcitabine and mitomycin C in patients with recurrence after BCG or BCG plus IFN alpha (all with intermediate or high risk NMIBC) conferred a RFS of 37% at a median followup of 22 months.²⁷ The sequential multi-agent chemotherapy regimen in this phase I clinical trial was based on our preclinical studies of intravesical treatments in a genetically engineered mouse model of bladder cancer.^{14,30} Our preclinical study of single and combination regimens of intravesical cisplatin, gemcitabine and docetaxel showed that mice receiving any 2-drug combination had a statistically significant delay in overt tumor formation, as well as reduced development of overt metastases compared to the single agent treatments.¹⁴ The participants in this trial represent a particularly high risk group. All were categorized as BCG unresponsive except for 1. They were also highly pretreated. The mean number of rounds of intravesical therapies

before enrollment was 3.7. Half of the study group had been treated with some form of salvage chemotherapy in addition to 2 BCG cycles and 7 had participated in previous phase I clinical trials. Despite this risk profile our results include the highest reported CR and PR rates (89% and 94%, respectively) and 1-year RFS (83%) of any phase I trial. With a median followup of 27.8 months only 3 of 18 patients had recurrence at 1 year (RFS 83%) and 2 of these were only within the prostatic urethra. Estimated 2-year RFS was 83%. At last followup 7 patients (39%) had recurrence, with an overall median time to recurrence of 21.8 months (range 2.6 to 27.1). For the remaining 11 patients without recurrence median followup time was 24.5 months (range 16.3 to 40.1). Although the majority of patients experienced at least 1 grade 1 or 2 AE, there were no higher grade toxicities observed.

Avoiding cystectomy represents a particularly significant end point for patients with high risk bladder cancer. Cystectomy-free survival at 1 year was 94% and at 2 years it was estimated to be 81%. At last followup 5 of 18 patients (28%) have undergone radical cystectomy with a median time to surgery of 18 months. Notably, 3 of these patients had no residual carcinoma in the bladder, as 2 had prostatic urethral disease and 1 had ureteral disease only. However, pathology at cystectomy showed significant disease progression. One patient had pT3 disease in the bladder and prostatic urethra, 1 had pT4 disease with involvement of the prostatic glands/stroma and 3 had positive lymph node involvement. Development of node positive disease carries a significantly worsened prognosis. Therefore, it is imperative that the risk of disease progression caused by delaying potentially curative cystectomy, especially in high risk patients, be seriously considered against the perceived benefits of avoiding cystectomy with salvage intravesical therapy.

The current study has several limitations. As a single institution study with a small cohort of 18 patients, conclusions regarding efficacy must be made with caution. Furthermore, while patients under study underwent robust surveillance with cystoscopy and urine cytology every 3 months, pathological stage cannot be fully assessed in patients who have not undergone radical cystectomy, thereby creating the risk of underestimating recurrence. In addition, the logistical difficulty of instillations 2 to 3 times per week during a 6-week induction period may affect the acceptance of this regimen. Lastly, our results may also serve as caution regarding enrolling patients with prostatic urethral disease, as 2 of the 3 patients enrolled with such disease had recurrence within the same location, and at the time of cystectomy node positive disease developed in 1 (Appendix 2).

CONCLUSIONS

Patients with BCG unresponsive or recurrent/relapsing NMIBC who are unwilling or unfit to undergo radical cystectomy currently have limited effective therapeutic options. The results of the current study demonstrate the safety and potential efficacy of a sequential intravesical cabazitaxel, gemcitabine and cisplatin regimen in a high risk group. It is well tolerated and yields a remarkable initial CR rate of 89% and 1-year RFS of 83%. Larger cohort studies with long-term followup are needed to validate these promising results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1.: Previous intravesical treatments

Previous Intravesical Therapies Per Patient

- 1 BCG (6) + BCG (6) → Gemcitabine/Everolimus (trial)
- 2 BCG (6) + BCG (3) → BCG/IFN (3) → Abraxane (trial) → Mitomycin (6) → BCG (6) + BCG 3 → Nab/Rapamycin (trial)
- 3 BCG (6) + BCG (6) → Gemcitabine (6) → BCG (6) → Mitomycin (6) → Valrubicin (6)
- 4 BCG (6) + BCG (6) → BCG/IFN (6) + BCG (6) → Nab/Rapamycin (trial) → Docetaxel (6)
- 5 BCG (6) + BCG (6) → Gemcitabine/Everolimus (trial) → BCG/IFN (6)
- 6 BCG (6) + BCG (3) → BCG (6)
- 7 BCG (6) + BCG/IFN (6) → Nab/Rapamycin (trial)
- 8 BCG (6) + BCG (6) → Gemcitabine/Everolimus (trial)
- 9 BCG (6) + BCG (6)
- 10 BCG (6) + BCG/IFN (6)
- 11 BCG (6) + BCG (3)
- 12 BCG (6) + BCG (6)
- 13 BCG (6) + BCG (3) + BCG (3) → Vicinium (trial)
- 14 BCG (6) + BCG (3) + BCG (3) + BCG (6)
- 15 BCG (6) + BCG (6) + BCG (3) + BCG (3)
- 16 BCG (6) + BCG (6)
- 17 BCG (6) + BCG (6) + Mitomycin (6) + Gemcitabine (6)
- 18 BCG 6 + BCG/IFN 6

Appendix 2.: Clinical and pathological characteristics at recurrence

Subject No.	Stage/Grade at Enrollment	Pathology at Recurrence	Cystectomy Stage	Cystectomy Notes
1	HG T1 + CIS	CIS	No cystectomy performed	No cystectomy performed
3	HG T1 + CIS	CIS	pT3N1	No intravesical disease, ureteral involvement only
4	HG T1 + CIS	TaHG	pT4aN2	Bladder and prostatic stromal involvement
5	HG T1, CIS @ PU	CIS in PU	pT3N1	No intravesical disease, PU involvement only
7	HG Ta + CIS	Ta HG	No cystectomy performed	No cystectomy performed

Subject No.	Stage/Grade at Enrollment	Pathology at Recurrence	Cystectomy Stage	Cystectomy Notes
8	HG T1, CIS @ PU	CIS, T1HG in PU	pT4N0	No intravesical disease, PU involvement only
9	HG Ta + CIS	CIS	pT2N0	Bladder and prostatic urethral involvement

Abbreviations and Acronyms

AE	adverse event
BCG	bacillus Calmette-Guérin
CGC	cisplatin, gemcitabine, cabazitaxel
CIS	carcinoma in situ
CR	complete response
DLT	dose limiting toxicity
HG	high grade
IFN	interferon
NMIBC	nonmuscle invasive bladder cancer
PR	partial response
PU	prostatic urethra
RFS	recurrence-free survival

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R et al.: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*2015; 136: E359. [PubMed: 25220842]
2. National Cancer Institute: Cancer Stat Facts: Bladder Cancer. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available at <https://seer.cancer.gov/statfacts/html/urinb.html>.
3. Sylvester RJ, Brausi MA, Kirkels WJ et al.: Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol*2010; 57: 766. [PubMed: 20034729]
4. Oddens J, Brausi M, Sylvester R et al.: Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol*2013; 63: 462. [PubMed: 23141049]
5. Lamm DL, Blumenstein BA, Crissman J et al.: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group study. *J Urol*2000; 163: 1124. [PubMed: 10737480]

6. Bohle A and Bock PR: Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004; 63: 682. [PubMed: 15072879]
7. Babjuk M, Bohle A, Burger Met al.: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol* 2017; 71: 447. [PubMed: 27324428]
8. Cambier S, Sylvester RJ, Collette Let al.: EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non-muscle-invasive stage Ta-T1 urothelial bladder cancer patients treated with 1–3 years of maintenance bacillus Calmette-Guerin. *Eur Urol* 2016; 69: 60. [PubMed: 26210894]
9. Isbarn H, Jeldres C, Zini Let al.: A population based assessment of perioperative mortality after cystectomy for bladder cancer. *J Urol* 2009; 182: 70. [PubMed: 19447427]
10. Shabsigh A, Korets R, Vora KCet al.: Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol* 2009; 55: 164. [PubMed: 18675501]
11. Steinberg G, Bahnson R, Brosman Set al.: Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol* 2000; 163: 761. [PubMed: 10687972]
12. Skinner EC, Goldman B, Sakr WAet al.: SWOG S0353: phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guérin. *J Urol* 2013; 190: 1200. [PubMed: 23597452]
13. Milbar N, Kates M, Chappidi MRet al.: Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients with non-muscle invasive bladder cancer. *Bladder Cancer* 2017; 3: 293. [PubMed: 29152553]
14. Delto JC, Kobayashi T, Benson Met al.: Preclinical analyses of intravesical chemotherapy for prevention of bladder cancer progression. *Oncotarget* 2013; 4: 269. [PubMed: 23563166]
15. Tamiya M, Kuhara H, Hirashima Tet al.: Hypersensitivity reactions associated with platinum-containing antineoplastic agents for thoracic malignancies. *Anticancer Res* 2011; 31: 4525. [PubMed: 22199326]
16. Fukui M, Penson RT, Krishna Vet al.: Carboplatin and cisplatin hypersensitivity—pattern, potential mechanism, and desensitization. *J Allergy Clin Immunol* 2004; 113: S72.
17. O'Quigley JO and Shen LZ: Continual reassessment method: a likelihood approach. *Biometrics* 1996; 52: 673. [PubMed: 8672707]
18. Jia XY, Ivanova A and Lee SM: Selection of the initial design for the two-stage continual reassessment method. *J Biopharm Stat* 2017; 27: 495. [PubMed: 28300466]
19. Lee SM and Cheung YK: Model calibration in the continual reassessment method. *Clin Trials* 2009; 6: 227. [PubMed: 19528132]
20. Lee SM and Cheung YK: Calibration of prior variance in the Bayesian continual reassessment method. *Stat Med* 2011; 30: 2081. [PubMed: 21413054]
21. Donohue JP, Einhorn LH and Perez JM: Improved management of nonseminomatous testis tumors. *Cancer* 1978; 42: 2903. [PubMed: 569545]
22. Sternberg CN, Yagoda A, Scher HIet al.: Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989; 64: 2448. [PubMed: 2819654]
23. McKiernan JM, Masson P, Murphy AMet al.: Phase I trial of intravesical docetaxel in the management of superficial bladder cancer refractory to standard intravesical therapy. *J Clin Oncol* 2006; 24: 3075. [PubMed: 16809732]
24. Laudano MA, Barlow LJ, Murphy AMet al.: Long-term clinical outcomes of a phase I trial of intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to standard intravesical therapy. *Urology* 2010; 75: 134. [PubMed: 19913890]
25. Dalbagni G, Russo P, Bochner Bet al.: Phase II trial of intravesical gemcitabine in bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. *J Clin Oncol* 2006; 24: 2729. [PubMed: 16782913]

26. McKiernan JM, Holder DD, Ghandour RA et al.: Phase II trial of intravesical nanoparticle albumin bound paclitaxel for the treatment of nonmuscle invasive urothelial carcinoma of the bladder after bacillus Calmette-Guérin treatment failure. *J Urol* 2014; 192: 1633. [PubMed: 24996128]
27. Cockerill PA, Knoedler JJ, Frank I et al.: Intravesical gemcitabine in combination with mitomycin C as salvage treatment in recurrent non-muscle-invasive bladder cancer. *BJU Int* 2016; 117: 456. [PubMed: 25682834]
28. Lightfoot AJ, Breyer BN, Rosevear H et al.: Multi-institutional analysis of sequential intravesical gemcitabine and mitomycin C chemotherapy for non-muscle invasive bladder cancer. *Urol Oncol* 2014; 32: 35.e15.
29. Steinberg RL, Nepple KG, Velaer K et al.: Quadruple immunotherapy of bacillus Calmette-Guerin, interferon, interleukin-2, and granulocyte-macrophage colony-stimulating factor as salvage therapy for non muscle-invasive bladder cancer. *Urol Oncol* 2017; 35: 670.
30. Puzio-Kuter AM, Castillo-Martin M, Kinkade CW et al.: Inactivation of p53 and Pten promotes invasive bladder cancer. *Genes Development* 2009; 23: 675. [PubMed: 19261747]

Figure 1.
Estimated RFS for all subjects

Figure 2.
Estimated RFS for subjects receiving maximum CGC dose.

Figure 3.
Clinical outcomes for each subject according to dose schedule

Table 1.

Doses of CGC evaluated for induction phase

Dose Level	Gemcitabine (mg)	Cabazitaxel (mg/100 ml saline)	Cisplatin (mg/100 ml saline) *
1	2,000	2.5	Not applicable
2	2,000	5	Not applicable
3	2,000	5	66
4	2,000	5	80
5	2,000	5	100

*
Dosed every other week.

Table 2.

Patient characteristics

Median age (range)	73	(44–88)
No. sex (%):		
Female	4	(22)
Male	14	(78)
No. stage/grade at enrollment (%):		
CIS only	3	(17)
HG T1 in PU	1	(6)
HG T1 + CIS	3	(17)
HG T1 + CIS in PU	2	(11)
HG Ta	4	(22)
HG Ta + CIS	5	(28)
No. previous intravesical therapies (%):		
2	6	(33)
3	7	(39)
4	2	(11)
5 or More	3	(17)
Median per type of previous intravesical therapy (range)	3	(2–8)

Table 3.

Frequency of adverse events

	No. Grade 1 (%)	No. Grade 2 (%)
Dysuria	9 (50)	3 (17)
Urinary urgency	6 (33)	3 (17)
Bladder spasm	1 (6)	3 (17)
Hematuria	4 (22)	0
Urinary incontinence	2 (11)	1 (6)
Urinary frequency	3 (17)	0
Skin ± subcutaneous tissue disorders - other	2 (11)	0
Reproductive system + breast disorders - other	2 (11)	0
Vaginal infection	0	1 (6)
Cystitis	1 (6)	0
Renal urinary disorders - other	1 (6)	0