



Oncolytic and immunotherapeutic CG0070 adenovirus for high-risk bacillus calmette-guerin unresponsive bladder cancer

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Abstract

Introduction To evaluate the response of patients with high-risk bacillus Calmette-Guerin (BCG)–unresponsive non-muscle invasive bladder cancer (NMIBC) who we treated with intravesical CG0070, a conditionally replicating granulocyte macrophage colony-stimulating factor (GM-CSF) containing an RB promoter.

Methods 15 patients with residual high grade BCG-unresponsive CIS +/- Ta/T1/T2 bladder cancer received one or more 6-week instillations of intravesical CG0070 and were retrospectively reviewed. Overall response including the number, location, grade and stage of recurrences, were recorded. Side effects of intravesical instillation of CG0070 were also investigated. 11 of the 15 patients had at least 2.5 years of follow up both before and after treatment, permitting statistical chi-square analysis for the 2.5 year pre- and post-CG0070 periods.

Results Of the 15 patients, 5 had Ta + Cis, 4 had T1 + CIS, 4 had CIS alone, and 2 had T2 + CIS prior to CG0070 instillation. Complete response of CIS was seen in 60% at 6 months, 47% at 12 months, and 40% at 24 months. Overall, 40% of patients remained tumor free and none progressed. For the 11 patients amenable to statistical analysis, 32 recurrences were noted within 2.5 years before therapy and 13 2.5 years after ($p < 0.01$). 40% of patients experienced no adverse events as a result of treatment. Most common side effects were hematuria (33.3%), malaise/fatigue (33.3%), and urgency/frequency (26.7%).

Discussion Treatment with intravesical CG0070 for high-risk BCG-unresponsive bladder cancer appears to be a promising salvage regimen worthy of further investigation.

Key words Non-muscle invasive bladder cancer; Oncolytic adenovirus; Intravesical therapy; BCG unresponsive

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Introduction

Non-muscle invasive bladder cancer (NMIBC) (stages Ta, T1, and T1S) accounts for approximately 70 percent of all new urothelial bladder cancer cases, recurs in up to 80 percent within 12 months when managed by transurethral resection of bladder tumors (TURBT) alone, and eventually progresses in stage in about 25 percent of patients [1]. Such high rates of recurrence and progression mandate additional therapy beyond TURBT. Current guidelines for management of NMIBC recommend TURBT (with repeat resection in T1 disease), followed by intravesical Bacillus Calmette-Guérin (BCG) for intermediate and high-risk patients [2-4]. Single-dose intravesical chemotherapy, often mitomycin, is recommended to be given in the immediate postoperative period following TURBT for low-grade papillary disease. Following TURBT for NMIBC, intravesical BCG is the current standard and has been shown to reduce disease recurrence, progression and mortality [5, 6]. Despite BCG, up to 40% of patients will eventually recur and remain at risk of progressive disease [6]. European Association of Urology (EAU) guidelines note that those who fail BCG are unlikely to respond to further BCG therapy and recommend radical cystectomy. Specifically, this includes patients who develop a muscle invasive bladder cancer (MIBC) at any time during follow up, those who develop a HG tumor during BCG therapy, those with HG NMIBC at 3 months following induction BCG, or those with HG recurrence after completion of BCG maintenance despite an initial response [2]. American Urological Association (AUA) guidelines offer similar recommendations, stating additional BCG should not be prescribed to patients intolerant of BCG or those that have recurrence of TURBT of HG NMIBC and/or CIS within 6 months of 2 induction courses of BCG or induction plus BCG maintenance. Furthermore, AUA guidelines recommend clinical trial enrollment for patients with persistent or recurrent intermediate or high-risk NMIBC who are unwilling or unfit for cystectomy after two courses of BCG [7]. Salvage intravesical treatments are an emerging option for such patients, although none at this point have been shown to have durable efficacy for BCG unresponsive patients. Thus far, only three additional intravesical therapies beyond BCG; doxorubicin, thiotepa and valrubicin; have been approved by the FDA and EMA for the treatment of bladder cancer, none of which have proven to be effective treatment options in the long-term [8].

To address this problem, viral gene therapy has been introduced as a potential solution for patients with NMIBC and BCG failure who do not undergo radical cystectomy. These viruses have the theoretical advantage of selective replication in tumor cells, leading to cell lysis and increased immune response to both oncolytic virions and tumor-specific antigens [9]. One such virus, CG0070, is a conditionally replicating adenovirus with an Rb promoter and human granulocyte macrophage colony-stimulating factor (GM-CSF) gene designed to take advantage of the defects in the retinoblastoma (Rb) pathway found in most cancers including urothelial carcinoma [10]. Here we present our institution's experience and response results in 15 patients with high-risk BCG-unresponsive NMIBC who were treated with at least one six-week course of intravesical CG0070.

Materials and Methods

Figure 1 is the progressing Flow-chart of the study.

Study population and design

Patients who received at least one six-week course of intravesical CG0070 were identified (n=15) and retrospectively reviewed. Post CG0070 number, location, grade and stage of recurrences,

progression to muscle invasion/metastasis, and overall length of follow up were recorded, as well as all cause and bladder-cancer specific survival. Side effects occurring post intravesical instillation were noted. Inclusion criteria specified patients with pathologically-confirmed NMIBC who had received at least two or more prior courses of intravesical therapy per recommended schedules, of which at least one therapy was BCG. The first course of BCG required at least 6 weekly treatments, and the second course required at least 2 weekly treatments. The term BCG unresponsive is defined as patients with BCG refractory disease (failure to achieve disease-free state at 6 months following initial BCG therapy with either maintenance or retreatment at 3 months because of persistent or rapidly recurrent tumor), BCG-resistant (rapid recurrence/persistence at 3 months), or BCG-relapsing disease (recurrence of disease after achieving disease free-state by 6 months). Patients with previous systemic chemotherapy or radiation therapy for bladder cancer, those with a history of an immunocompromised state, those on immunosuppressive or immunomodulatory agents, and those with a history of other clinically-significant malignancy were excluded. This IRB-approved study is a part of a larger single-arm, phase II, multicenter study (clinicaltrials.gov NCT02365818) assessing the safety and efficacy of CG0070 in patients with NMIBC who have failed BCG therapy and refused cystectomy [11]. These 15 patients were included in the latest interim analysis of the multicenter study [12]. Special permission was obtained from Cold Genesys to retrospectively review the patients from our institution who had received intravesical CG0070.

Study Variables

The following variables were collected from patients' medical records: gender, age, ethnicity, tobacco exposure, the initial date and stage/grade of bladder cancer diagnosis, the number and stage/grade of recurrences before CG0070 treatment, date of CG0070 treatment(s), side effects experienced while undergoing CG0070 therapy, the number and stage/grade of recurrences after CG0070 treatment, involvement (if any) of bladder cancer in bladder diverticula, deBruhn nest, prostatic urethra or upper tract in initial diagnosis of bladder cancer or on subsequent recurrences, length of follow up from date of CG0070 treatment to last cystoscopy, the length of follow up from date of CG0070 treatment to last documented patient encounter, and date and cause of mortality.

CG0070 Treatment Protocol

Patients received 6 weekly instillations of intravesical CG0070 on days 1, 8, 15, 22, 29, and 36 at dose levels ranging from 1 * 10¹² to 3 * 10¹³ viral particles (vp), using the same dose for all 6 treatments. Pretreatment of 5% DDM, a nonionic surfactant

Table 1. Baseline Characteristics.

Items	Number
Number of patients	15
Age, years (median)	71.5
Caucasian race, n (%)	14 (93%)
Smoke Exposure, n (%)	12 (80%)

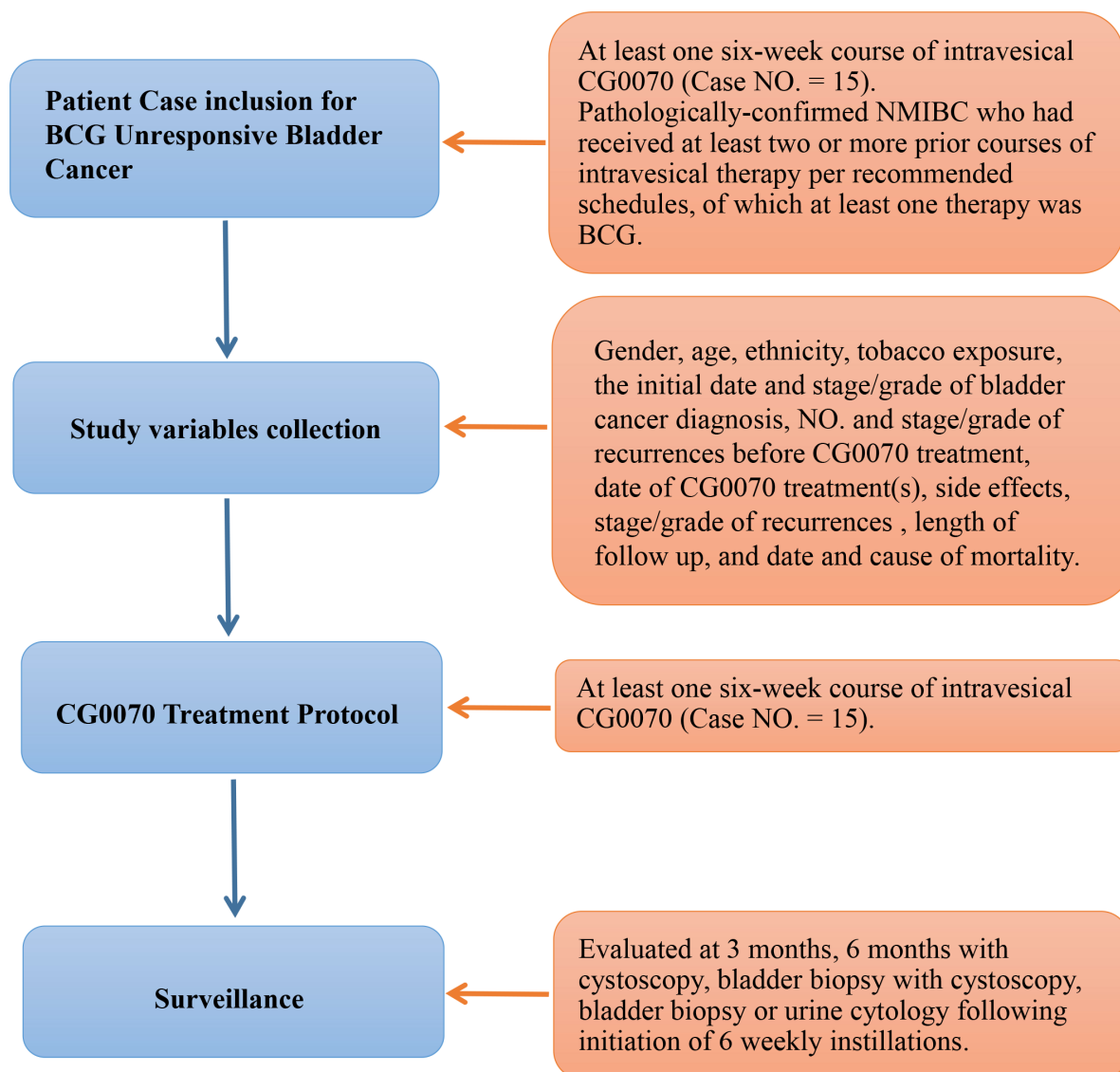


Figure 1. Progressing Flow-chart of the study.

transduction agent that acts as a mild detergent and solubilizing agent, was given via a 100% silicone catheter. Pretreatment consisted of an intravesical wash with 100 ml normal saline, followed by an intravesical wash with 75 mL of 0.1% DDM. Patients then received intravesical instillation of 100 mL of 0.1% DDM, which was retained in the bladder for 15 minutes, followed by a subsequent rinse with 100 mL of saline. Following pretreatment, CG0070 in 100 mL saline was instilled for dwelling time of 45-50 minutes, during which the patient was repositioned from left side, right side, abdomen, and back every 10-12 minutes to maximize bladder surface exposure to CG0070. Patients were advised to limit fluid intake, hold medications unless medically necessary, and avoid caffeine for 8-24 hours prior to instillation and were asked to retain the medication in bladder for recommended time period.

Surveillance

Following initiation of 6 weekly instillations, patients were evaluated at 3 months with cystoscopy, bladder biopsy if lesions

were seen, and urine cytology. At 6 months, patients underwent cystoscopy and random biopsies if no visible tumor was present to evaluate for treatment response. Patients were then followed every 3 months with cystoscopy, biopsy if lesions seen, and urine cytology. After initial demonstration of safety, patients received further 6 week courses of maintenance intravesical CG0070 following the 6 month evaluation. If recurrence was found further treatment could include but was not limited to CG0070. Recurrence was defined by pathologically confirmed disease following bladder biopsy, TURBT, or office ablation for small tumors with a positive urine cytology. A positive urine cytology alone was not criteria for recurrence.

Statistical Analysis

Statistical analysis and methodology was loosely based on Morales et al. original documentation of intravesical BCG in the treatment of superficial bladder tumors [13]. Similar to their problem, wide variation in pre-and post-CG0070 treatment periods invalidates traditional statistical analysis for all 15 subjects in our study. To

Table 2. Results of CG0070.

Pre-CG0070		Post-CG0070	
Total Recurrences Before	92 +	Total Recurrences After	22
Highest Stage, n (%)		Highest Stage, n (%)	
Ta + CIS	5 (33%)	No recurrence Overall	6 (40%)
T1 + CIS	4 (27%)	at 6 months	9 (60%)
CIS alone	4 (27%)	at 12 months	7 (47%)
T2 + CIS	2 (13 %)	at 24 months	6 (40%)
		CIS alone	5 (33%)
		HG T1 + CIS	2 (13%)
		Prostatic HG Ta + CIS	2 (13%)
		Progression	0
		Deaths unrelated to bladder cancer	2
		Death of unknown cause	1
Recurrences 2.5 years before*	32	Recurrences 2.5 years after*	13 (p<0.01)
Highest Stage, n (%)		Highest stage, n (%)	
CIS alone	5 (45%)	No recurrence	5 (45%)
Ta + CIS	3 (27%)	CIS alone	3 (18%)
T1 + CIS	2 (18%)	Prostatic HG Ta + CIS	2 (18%)
T2 + CIS	1 (9%)	HG T1 + CIS	1 (9%)

*Amenable to statistical analysis

address this, 11 of the 15 patients had at least 2.5 years of follow up both before and after treatment of CG0070. As such, an analysis was done on these 11 patients for recurrences 2.5 years before and after instillation of CG0070. A chi-square test was conducted for these 11 patients for the 2.5 year pre-CG0070 and 2.5 year post-CG0070 periods.

Results

Baseline characteristics of all 15 patients reviewed in this study are described in **Table 1**. Median age was 71.5 years and all but one patient were Caucasian. 12/15 (80%) of subjects had current or prior smoke exposure.

The total number of recurrences before and after CG0070 treatment are described in **Table 2**. Greater than 92 recurrences were noted for all 15 patients prior to CG0070 exposure. 100% of patients had CIS prior to CG0070 administration. 4 patients (27%) had CIS alone, 5 (33%) had Ta + CIS, 4 (27%) had T1 + CIS, and

2 (13%) had prior T2 and persistent CIS. Following treatment of CG0070 there were 22 recurrences, a 76% decrease in bladder cancer recurrences overall. Six patients (40%) had no recurrence following therapy, 5 (33%) had recurrence of CIS alone, 2 (13%) had HG Ta + CIS. Three had these recurrences in prostatic tissue. Two (13%) had HG T1 + CIS recurrence but no patient had progression of their bladder cancer. Complete response of CIS was seen in 9 patients (60%) at 6 months, 7 (46.7%) at 12 months, and 6 (40%) at 24 months.

Despite these findings, wide variation in pre-and post-CG0070 treatment periods precludes traditional statistical analysis for the data described above. To address this, 11 of the 15 (73%) patients had at least 2.5 years of follow up both before and after treatment of CG0070. Of the four patients that did not have at least 2.5 years of follow up, 1 was lost to follow up and 3 patients died, 2 of which died of a cause unrelated to bladder cancer and 1 died of an unknown cause. Considering the patients who were evaluable for 2.5 year follow up, 5 (45%) patients had highest stage of recurrence

Table 3. 2.5 year CG0070 timetable.

Pt	Pre-CG0070			CG0070			Post-CG0070			
	-2.5 Years	-2.0 Years	-1.5 Years	-1.0 Years	-0.5 Years	0.5 Years	1.0 Years	1.5 Years	2.0 Years	2.5 Years
1			HG T1		HG CIS					
2			HG Ta*	HG CIS bladder & prostate HG CIS prostate		HG CIS Prostate				LG Ta bladder/ HG Ta Prostate Positive cytology CIS*****
3		HG T2/CIS	HG Ta	HG CIS R UO		HG T1				
4	HG CIS		HG CIS	LG Ta/CIS**						
5			In-office ablation HG Ta	HG CIS						
6		HG T1	HG T1	HG T1/CIS	HG T1/Ta CIS			HG Ta + CIS HG Ta	CIS	
7				HG CIS bladder & prostate		CIS				
8			HG Ta HG CIS	HG CIS	HG CIS					
9			HG Ta & CIS Bladder, CIS prostate	HG Ta/CIS	HG Ta Bladder & L UO	HG Ta/CIS	CIS L UO	HG Ta/CIS Bladder and Prostate*** HG CIS R Kidney****		
10	HG T1/CIS, HG CIS			HG CIS						
11				CIS		CIS				

* HG Ta in bladder and prostatic urethra;

** LG Ta and CIS with involvement of prostate and Left Ureteral Orrifice;

***S/P Radical cystectomy with neoadjuvant chemo;

****S/P nephroureterectomy;

*****S/P in-office ablation.

Table 4. Side Effects.

CG0070 Side Effects	Number (% Frequency)
None	6 (40%)
Hematuria	5 (33.3%)
Malaise/fatigue	5 (33.3%)
Urgency/Frequency	4 (26.7%)
Dysuria	3 (20%)
Flank pain	2 (13.3%)
Fever	2 (13.3%)
Flu like symptoms	1 (6.7%)
Abd pain	1 (6.7%)
Nausea	1 (6.7%)
Abdominal Rash	1 (6.7%)

being CIS alone, 3 (27%) had Ta + CIS, 2 (18%) had T1 + CIS, and 1 (9%) had T2 + CIS prior to CG0070 treatment. 32 recurrences were noted before therapy whereas only 13 recurrences were recorded after, accounting for a statistically significant difference ($p < 0.01$). After treatment 5 (45%) patients experienced no recurrence, 3 (27%) experienced CIS alone, 2 (18%) experienced stage of Hg Ta + CIS, and only 1 (9%) had HG T1 + CIS.

A complete breakdown regarding the time points stage of recurrences 2.5 years before and after CG0070 therapy are demonstrated in **Table 3**.

Side effects experienced during the 6 week treatment period are described in figure 4. Six patients (40%) experienced no symptoms related to the treatment. Hematuria and generalized malaise or fatigue were the most common side effects experienced with 33.3%, followed by urgency or frequency (26.7%) and dysuria (20%). All 15 patients completed the 6 week therapy. For those that did experience side effects, none had to interrupt the therapy because of the severity of side effects (**Table 4**).

Discussion

Few options other than radical cystectomy exist for patients with high risk NMIBC who fail BCG therapy. With advancing age many are poor surgical candidates, and advanced age increases the mortality and decreases the efficacy of cystectomy. Young as well as old patients refuse the procedure. Randomized trial of radiation therapy for high grade, T1 NMIBC failed to show benefit [14]. Chemoradiation has been more encouraging but data on BCG failure in NMIBC are not available. The FDA-approved treatment, valrubicin (Valstar), in a highly pretreated CIS population had only 16.4% of patients remaining disease free at one year [15]. One year recurrence free survival (DFS) in NMIBC BCG failure patients are 21-28% for intravesical gemcitabine, 36% for Abraxane, 40-50% for docetaxel, 48% for combination gemcitabine and Mitomycin C, 54% for combination gemcitabine and docetaxel, and 69% for hyperthermic Mitomycin C [16]. Viral gene therapy offers a potential new solution for BCG unresponsive patients, filling the

hole that approved intravesical therapies thus far have not yet fully addressed.

CG0070, a conditionally replicated GM-CSF-armed oncolytic adenovirus, takes advantage of the RB pathway defect in urothelial carcinoma to induce cytotoxicity of tumor cells while simultaneously increasing the immune response to both oncolytic virions and tumor-specific antigens [9, 10]. Our experience with CG0070 suggests that this form of treatment may alter the recurrence pattern of high-risk, treatment resistant disease. Considering the recurrent shortages of BCG and the observation that to date CG0070 appears to have no significant adverse or long-lasting side effects, this treatment could become a welcome advance in the treatment of NMIBC.

When compared to other emerging treatments for BCG unresponsive NMIBC, particularly among other viral gene therapies, our results demonstrate comparable or superior efficacy despite a higher risk patient population with 100% of patients having CIS, and others having prostatic, upper tract and even prior muscle involvement. Instiladrin (rAD-IFN[alpha]/Syn3) is another adenovirus currently in phase III trials that reported 35% of 43 patients with high grade BCG refractory bladder cancer remained disease free at one year [17]. Another viral gene therapy, ALT-801, a recombinant fusion protein consisting of IL-2 linked to a T-cell-receptor domain that can recognize a peptide of the p53 antigen, is currently being tested in combination with gemcitabine in a phase Ib/II trial with preliminary results demonstrating a complete durable response >12 months in 2 of 6 patients [16].

This study is limited by its retrospective design and lack of a comparison control. Furthermore, it is important to note that our results reflect just our single institution's experience with CG0070 and therefore are not necessarily reflective of other institutions using CG0070. Our relatively small cohort size reduces the power of statistical analysis. Additionally, 93% of our patients were Caucasian and 93% were male, creating a fairly restricted distribution of sex and ethnicity.

Conclusion

In summary, treatment with intravesical CG0070 for high-risk BCG-unresponsive NMIBC appears to be a well-tolerated salvage regimen with promising results in reducing tumor recurrence and progression. Our results demonstrate comparable success rates compared to other viral gene therapies in a high-risk patient population. Further investigation of CG0070 is warranted to optimize treatment for patients with BCG-resistant NMIBC.

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Ethical policy

This IRB approved study is a part of a larger single-arm, phase II, multicenter study (clinicaltrials.gov NCT02365818) assessing the safety and efficacy of CG0070 in patients with NMIBC who have failed BCG therapy and refused cystectomy. These 15 patients were included in the latest interim analysis of the multicenter study. Special permission was obtained from Cold Genesys to retrospectively review the patients from our institution who had received intravesical CG0070.

Author contributions

EA: performed the majority of the retrospective review, data analysis, and drafted the manuscript. DM: assisted with the retrospective review and methodology and regulatory compliance for the study. JT: also assisted with the retrospective review and assisted in the initial CG0070 treatment protocol in compliance with the original single-arm, phase II, multicenter study (clinicaltrials.gov NCT02365818). DL: is the principal investigator for the project and oversaw all aspects of the project and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests

All authors declare no competing interests.

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References

1. Soukup V, Čapoun O, Cohen D, et al: Prognostic Performance and Reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in Non-muscle-invasive Bladder Cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review. *Eur Urol* 2017, 72(5): 801-813.
2. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al: EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol* 2017, 71: 447-461.
3. MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC, et al: Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007, 178: 2314-2330.
4. Brausi M, Witjes JA, Lamm D, Persad R, Palou J, Colombel M, et al: A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the International Bladder Cancer Group. *J Urol* 2011; 186: 2158-2167.
5. Böhle A, Bock P: Intravesical bacille calmette-guérin versus mitomycin c in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004, 63(4): 682-686.
6. Sylvester RJ, van der Meijden APM, Lamm DL: Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002, 168: 1964-1970.
7. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, Pruthi R, Quale DZ, Ritch CR, Seigne JD et al: Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol* 2016, 196(4): 1021-1029.
8. Kamat AM, Colombel M, Sundi D, Lamm D, Boehle A, Brausi M, et al: BCG-unresponsive non-muscle-invasive bladder cancer: recommendations from the IBCG. *Nat Rev Urol* 2017, 14(4): 244-255.
9. Ramesh N, Ge Y, Ennist DL, Zhu M, Mina M, Ganesh S, & Seshidhar Reddy P: CG0070, a Conditionally Replicating Granulocyte Macrophage Colony-Stimulating Factor -- Armed Oncolytic Adenovirus for the Treatment of Bladder Cancer. *Clin Cancer Res* 2006, 12(1): 305-313.
10. Sherr CJ, McCormick F: The Rb and p53 pathways in cancer. *Cancer Cell* 2002, 2(2): 103-112.
11. Burke JM, Lamm DL, Meng MV, Nemunaitis JJ, Stephenson JJ, Arseneau JC, Aimi J, Lerner S, Yeung AW, Kazarian T, Maslyar DJ, McKiernan JM: A first in human phase I study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. *J Urol* 2012, 188(6): 2391-2397.
12. Packiam VT, Lamm DL, Barocas DA, Trainer A, Fand B, Davis RL 3rd, Clark W, Kroeger M, Dumbadze I, Chamie K, Kader AK, Curran D, Gutheil J, Kuan A, Yeung AW, Steinberg GD: An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: Interim results. *Urol Oncol* 2018, 36(10): 440-447.
13. Morales A, Eiding D, & Bruce AW: Intracavitary Bacillus Calmette-Guerin in the Treatment of Superficial Bladder Tumors. *J Urol* 2017, 197(2): S142-S145.
14. Harland SJ, Kynaston H, Grigor K, Wallace DM, Beacock C, Kockelbergh R, Clawson S, Barlow T, Parmar MK, Griffiths GO: National Cancer Research Institute Bladder Clinical Studies Group. A randomized trial of radical radiotherapy for the management of pT1G3 NXM0 transitional cell carcinoma of the bladder. *J Urol* 2007, 178(3 Pt 1): 807-813.
15. Steinberg G(1), Bahnson R, Brosman S, Middleton R, Wajsman Z, Wehle M: Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol* 2000, 163(3): 761-767.
16. Hassler MR, Shariat SF, & Soria F: Salvage therapeutic strategies for bacillus Calmette-Guerin failure. *Current Opinion in Urology* 2019, 29(3): 239-246.
17. Shore ND, Boorjian SA, Canter DJ et al: Intravesical rAd-IFN α /Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin-Refractory or Relapsed Non-Muscle-Invasive Bladder Cancer: A Phase II Randomized Study. *J Clin Oncol* 2017, 35(30): 3410-3416.