

Review

CIS of the Bladder: Significance and Implications for Therapy

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Abstract.

Purpose of the review: To review the most recent literature with regards to the pathogenesis, diagnostics, clinical implications and treatment strategies for Carcinoma *in Situ* (CIS) of the Bladder.

Recent findings: There have been advancements in understanding the genetic composition and biochemical behavior of CIS. Technological advancements including Photodynamic Diagnosis (PDD) with Hexaminolevulinat (HVA) better detect CIS compared to traditional white light (WL) cystoscopy. Recently published single and multi-center studies have enabled better understanding of the impact of CIS on clinical and cancer related outcomes, including disease recurrence and patient survival. Alternative intravesical chemotherapeutic and immunotherapies for CIS have been investigated, especially in the setting of Bacillus Calmette-Guerin (BCG) unresponsive disease. While these demonstrate a great deal of promise, they have not garnered much success.

Summary: The genetics of CIS is linked to aggressive, and at times resistant disease, with increased cancer progression and associated clinically worse cancer specific outcomes. New technologies have enabled a more effective diagnosis of CIS. The development of a standardized definition for clinical trials and greater disease understanding will enable us to develop better treatment options.

Keywords: Carcinoma *in situ*, bladder cancer, transitional cell carcinoma, NMIBC, BCG

INTRODUCTION

Bladder Cancer represents the 6th most common cancer diagnosis in 2018, accounting for 4.7% of all new cancer cases [1]. Around 70% of new diagnoses represent Non-Muscle Invasive Bladder Cancer (NMIBC), of which 10% are CIS [2]. The untreated natural history of CIS is progression to Muscle Invasive Bladder Cancer (MIBC) in 50% of cases at 5 years [3, 4]. If treated, progression is 30–40%

at 10 years [3, 4]. The current standard of care for CIS is induction and maintenance BCG [5]. If the disease responds to induction therapy, maintenance therapy should be continued for 3 years as this has been shown to be superior to induction therapy alone and to induction plus one year of maintenance [4, 6].

Great efforts have been devoted to understanding the molecular biology of CIS. Due to its high-grade nature, it is characterized by more chromosomal alterations than low grade disease [7]. Various groups have classified tumors based on their genetic profile and molecular expression rather than histology [8–10]. Dyrskjøt and colleagues found that CIS has a characteristic molecular profile, as does NMIBC with surrounding CIS compared to NMIBC without CIS [10]. Hedegaard et al. found that a certain molecular

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profile was associated with increased progression to MIBC. There was a higher prevalence of CIS samples in this high-risk progression group [8].

New advancements in optical and video technology help more accurately identify CIS which is not visible by white light in up to 50% of patients [11]. CIS associated with Ta or T1 high-grade cancers implies a more aggressive diathesis with higher probability of progression [12]. Photodynamic diagnosis (PDD) and Narrow Band Imaging (NBI) both improve detection of CIS lesions [13]. Multiple phase III studies and meta-analyses have found that PDD and NBI increase CIS detection compared to using WL cystoscopy alone [14–16].

As molecular and diagnostic advancements continue to be made, recent studies have focused on understanding the effect of CIS on cancer related outcomes. CIS in Radical Cystectomy (RC) specimens has been reported to be associated with increased disease recurrence and decreased pathologic complete response after neoadjuvant chemotherapy (NAC) [17–19]. Even though previous reports have linked complete pathological response to decreased cancer recurrence and increased overall survival (OS) [20], there have been conflicting reports as to whether CIS found in RC samples is associated with increased cancer-specific mortality (CSM) [17, 19].

Multiple trials have evaluated new therapies for CIS, particularly in the setting of BCG unresponsive disease. Many of these trials have been hampered by low patient recruitment and an inconsistent definition of CIS response to BCG prior to the establishment of unresponsive disease [21]. Although several checkpoint inhibitors have been approved for metastatic or locally advanced bladder cancer, Valrubicin remains the only intravesical agent approved by the FDA for treatment of BCG refractory or recurrent NMIBC since 1998 [22]. However, innovative trials using immunotherapy, oncolytic vectors and new chemotherapy combinations are underway and show promise for the treatment of CIS and other types of NMIBC [23–27].

In this review, we present the most current pathogenesis, diagnostics, clinical implications and treatment strategies for CIS. This article is exempt from Institutional Review Board review as it is a review article.

MOLECULAR BIOLOGY OF CIS

NMIBC is sub-classified according to histology and degree of tumor invasion. Tumors are either pap-

illary (Ta), confined to the mucosa (CIS) or invading into the lamina propria but not into the muscle (T1). CIS is considered a high-grade cancer due to its degree of cellular dysplasia and aggressive behavior [4].

A recent characterization of the molecular biology of CIS comes from Hedegaard and colleagues [8]. This multi-institutional trial characterized NMIBC into three molecular subtypes with the goal of identifying which patients with NMIBC would benefit from early RC. Class 1 was mostly composed of low grade urothelial tumors, which expressed early cell cycle genes and mutations in Fibroblast Growth Factor Receptor 3 (*FGFR3*). Class 2 tumors demonstrated high expression of late cell cycle genes and epithelial-mesenchymal transition associated genes. Class 3 tumors had a higher expression of primitive cytokeratins, which are markers for bladder cancer stem cells. Class 2 tumors had a high prevalence of CIS with a higher risk of progression to MIBC (25 out of 31 total progression events) when compared to class 1 and 3 tumors.

Heide and colleagues performed multiregional whole exome sequencing of ten RC samples [28]. The authors found APOBEC mutational signatures active in CIS; these appeared to be a source of mutations that persisted as the tumor evolved into invasive cancer. The investigators suggest that key alterations in invasive cancer are also acquired in CIS as both of these share up to 80% of mutations.

Dyrskjøt and colleagues performed microarray expression profiling to examine the gene expression patterns in NMIBC with surrounding CIS, without surrounding CIS, and in MIBC [10]. The authors reviewed biopsies of normal urothelium and urothelium with CIS lesions from the same bladder and constructed a 16-gene molecular CIS classifier. Interestingly, gene expression from NMIBC with surrounding CIS is similar to histologically normal samples adjacent to the CIS lesions. The CIS expression profile was also appreciated in MIBC samples.

Epigenetic alterations are also associated with lesions such as CIS. Scott et al. identified epigenetic alterations in urine cytology of patients with high grade NMIBC [29]. There were more alterations in chromatin regulating complexes among patients whose tumor was non-papillary on cystoscopy.

Other investigators have analyzed the immunobiology of CIS. Dowell et al. analyzed the effect of Interleukin (IL)-17 positive mast cells on CIS [30]. The investigators observed an increased number of these cells in the CIS environment compared to other

types of non-CIS NMIBC. Interestingly, patients with higher levels of IL17 after BCG therapy had a significantly longer event-free survival when compared to patients with lower IL17 positive cells. These studies suggest that understanding the biology of CIS may bring a more thorough understanding of tumor behavior compared to histologic diagnosis alone.

ADVANCES IN DIAGNOSIS OF CIS

There have been new developments in the diagnosis of CIS that parallel the molecular understanding of the disease. Bladder cancer has been traditionally diagnosed with WL cystoscopy. A recent study by Nkwam et al. evaluated the cancer detection rate of WL flexible and rigid cystoscopy in patients with a previous diagnosis of NMIBC [31]. They found a 23.5% cancer detection rate in intermediate and high risk NMIBC when performing biopsies of isolated red patches seen on WL cystoscopy.

Alternate technologies have been compared to the traditional WL cystoscopy [14–16]. Drejer et al. compared the use of WL cystoscopy, NBI and PDD in the diagnosis of flat dysplasia and CIS [14]. The authors instilled HVA and then proceeded with WL cystoscopy, followed by NBI and then PDD. They found a higher sensitivity but similar specificity when comparing NBI or PDD versus WL cystoscopy. No differences were appreciated when comparing NBI with PDD. A prospective randomized, open label study performed by Daneshmand et al. compared the use of PDD to WL cystoscopy in the outpatient office setting [15]. Patients who had suspicious findings on office cystoscopy were taken to the operating room for further assessment and biopsy. The authors found that 22% of patients had CIS which was detected with PDD but not with WL. A recent meta-analysis by Xiong et al. found a 31% increase in lesion detection rate when comparing NBI versus WL cystoscopy [16]. Recently, the use of fluorescent cystoscopy was recommended by the AUA NMIBC Guidelines to increase NMIBC detection and decrease cancer recurrence [5].

Emerging technologies can potentially help stratify cancer grade and stage. Probe-Based Confocal Laser Endomicroscopy (pCLE) can be used to visualize bladder CIS at the cellular level. This technique stains the cell nuclei and uses an imaging probe to visualize cancer cells during cystoscopy. Liem et al. performed pCLE in 62 patients with a total of 82 suspicious lesions in order to validate pCLE find-

ings with histology [32]. The authors concluded that evaluating pCLE cell organization, morphology and cell border definition helped establish high grade disease with a sensitivity of 80% and specificity of 66% using independent uro-pathologic histology as the gold standard. Of note, these features had moderate to substantial interobserver agreement. The authors were not able to extrapolate pCLE high grade results to patients with CIS as they only had two subjects with this pathology but stressed the importance of evaluating its use in the detection of CIS. Lee et al. performed a prospective study of 119 lesions, 21 of which were pathologically confirmed CIS, comparing pCLE findings to pathological specimens [33]. They found a 71.4% sensitivity and 81.3% specificity for the diagnosis of CIS using pCLE when compared to pathological specimens.

Huang et al. published a systematic review and meta-analysis of 9 articles including 402 patients regarding optical coherence tomography (OCT) in bladder cancer [34]. This technology works as an optical biopsy; ultrasound is used to provide cross-sectional images at a magnification of 10 μm , which is similar to histopathology slides. The authors report that this technology has a 96% sensitivity and 82% specificity for the diagnosis of early stage bladder cancer, including CIS, when compared to histopathology as the gold standard. These technologies are still in development and are not currently used in clinical practice for the diagnosis of bladder cancer.

CIS AND CANCER RELATED OUTCOMES

As we acquire a greater understanding of the molecular changes associated with CIS, there is a need to have precise information regarding the impact of the disease on clinical outcomes. Various studies have evaluated the impact of CIS on cancer related outcomes in both NMIBC and MIBC, as summarized in Table 1.

Concomitant CIS may affect cancer related outcomes in patients with MIBC who undergo RC. Thomas et al. studied the effect of concomitant CIS on patients who had NAC and RC performed for MIBC [18]. Patients were divided into cohorts with or without CIS associated with transurethral resection of bladder tumor (TURBT) specimens over a median period of 25.4 months. The primary outcome was the effect of CIS on pathological response after NAC in RC specimens. Secondary analysis included progression free survival (PFS) and overall survival (OS).

Table 1
Summary of CIS and cancer related outcomes

Study	Purpose	Summary
Thomas et al. [18]	Evaluate the effect of concomitant CIS on patients who had NAC and RC for MIBC	1) No CIS on TURBT specimens was associated with a 4-fold increase in complete pathologic response in RC specimens 2) No difference in OS or PFS
Vasdev et al. [35]	Evaluate the effect of concomitant CIS on patients who had NAC or induction chemotherapy followed by RC for MIBC	1) No effect of CIS on TURBT specimens with regards to OS or path CR
Parker et al. [17]	Evaluate the effect of CIS on path CR after NAC	1) Decreased CR on RC specimens in patients that had CIS on TURBT specimens (10.7% vs 26.3%, $p=0.02$) 2) No difference in RFS, OS or CSS
Amini et al. [36]	Impact of CIS on RFS and OS in patients treated with RC for curative intent	1) Patients with CIS had decreased 5-year RFS (67.7%) compared to no CIS (73%) ($p=0.031$), Similar OS. 2) No differences in RFS or OS when CIS was present in the subgroup that received NAC
Petrelli et al. [20]	Evaluation of survival benefit when achieving a path CR after NAC	1) 81% decrease in cancer recurrence 2) 55% decrease in death in patients with CR
Shariat et al. [37]	Assess whether presence of concomitant CIS has a detrimental effect on cancer control after RC	1) CIS was a predictor of disease recurrence in patients who underwent RC
Gupta et al. [38]	Assess the pathologic features and clinical outcomes of patients with clinical T1HG bladder cancer treated with RC	1) CIS was associated with increased recurrence (HR: 2.13, 95% CI: 1.14 to 3.98) and CSM (HR: 2.75, 95% CI: 1.17 to 6.46)
Moschini et al. [19]	Assess the incidence of CIS, its effect on disease recurrence and patient survival in patients treated with RC	1) CIS was associated with worse CSM in pT0-pT2 patients (HR =1.82; 95% CI: 1.01 to 3.29; $p=0.04$) but not in patients with pT3-pT4 disease 2) Concomitant CIS was associated with increased CR but no CSM or OM
Gontero et al. [39]	Assess prognostic factors in patients who received BCG as initial intravesical treatment of T1HG tumors	1) CIS on TURBT specimens was associated with earlier time to progression and time to recurrence
Giacalone et al. [40]	Report long-term outcomes of patients with MIBC treated by TMT.	1) CIS on TURBT specimens was associated with worsened OS (HR: 1.56, 95% CI: 1.17 to 2.08) and DSS (HR: 1.50, 95% CI: 1.03 to 2.17)
Kimura et al. [41]	Investigate the prognostic impact of concomitant CIS in RC specimens	1) CIS was associated to worse CSM (HR: 1.51; CI: 1.001 to 2.280), RFS (HR: 1.57; 95% CI: 1.12 to 2.21) in patients with organ confined cancer 2) CIS was associated with higher ureteral involvement in the complete cohort (OR: 4.51; 95% CI: 2.59 to 7.84)

The authors found that the absence of CIS on TURBT specimens was associated with a 4-fold increase in complete pathologic response. No statistically significant differences in terms of PFS or OS were found between subjects who did or did not have CIS on RC specimens. A recent analysis of 1213 patients by Vasdev et al. also evaluated the effect of concomitant CIS on patients who had NAC or induction chemotherapy followed by RC for MIBC [35]. CIS on TURBT specimens did not affect OS or complete pathologic response (pCR) to NAC or induction chemotherapy.

A multi-institutional retrospective review by Parker et al. also evaluated the effect of CIS on pCR

rate after NAC [17]. After controlling for pretreatment factors, the authors noted a decreased pCR on RC specimens in patients that had CIS on TURBT specimens. Similar to the previous study, the authors noted no statistically significant difference in other cancer related outcomes such as recurrence free survival (RFS), OS or cancer specific survival (CSS). The median follow-up was similar to the other study at 23.4 months.

Amini et al. performed a retrospective analysis regarding the impact of CIS on RFS and OS in 2518 patients treated with RC for curative intent (both NMIBC and MIBC) [36]. Patients with CIS had

decreased 5-year RFS (67.7%) compared to no CIS (73%) ($p=0.031$), but similar OS ($p>0.05$). There were no statistically significant differences in RFS or OS when CIS was present in the subgroup that received NAC.

Although these trials did not demonstrate differences in OS when comparing patients with or without presence of CIS on pathologic analysis, Petrelli et al. showed a survival benefit to achieving a pathological complete response after NAC in MIBC [20]. This was a meta-analysis of 13 trials involving 886 patients who received NAC and RC for treatment of bladder cancer. The study reported an 81% decrease in recurrence and 55% decrease in death in patients with pCR. Shariat et al. found CIS to be a predictor of disease recurrence in patients who underwent RC, especially those with organ confined disease [37]. This finding is supported by Gupta et al. who reported that the presence of CIS was associated with a two-fold increase in bladder cancer recurrence and an almost three-fold bladder increase in cancer-specific mortality (CSM) in patients who received treatment with RC for NMIBC [38].

Moschini et al. performed a retrospective review of 1128 patient charts to assess the incidence of CIS and its effect on disease recurrence and patient survival in patients treated with RC [19]. Patients had a median follow up of 6 years and patients who had NAC were excluded from analysis. The patients were stratified into subgroups consisting of pT0–pT2 disease and pT3–pT4. The presence of CIS was associated with worse CSM in pT0–pT2 patients but not in patients with pT3–pT4 disease. In the overall population, they observed that the presence of concomitant CIS was associated with increased recurrence but no changes in CSM or Overall Mortality (OM). Gontero et al. had similar findings in their multicenter retrospective review. The authors studied a cohort of 2451 patients with NMIBC treated with BCG [39]. CIS on TURBT specimens was associated with earlier time to progression and time to recurrence.

Giacalone et al. performed a retrospective analysis of 475 patients with MIBC treated with trimodal therapy (TURBT, Radiation and Chemotherapy) from 1986 to 2013 [40]. The authors evaluated response to chemoradiation, OS, disease specific survival (DSS), risk of salvage cystectomy and bladder intact-DSS. The presence of CIS on TURBT specimens was associated with worsened OS and DSS.

Kimura and colleagues performed a systematic review and meta-analysis of 23 studies including 20,647 patients that investigated the prognostic

impact of CIS in RC specimens [41]. CIS was associated to worse CSM (HR 1.51) and RFS (HR 1.57) in patients with organ confined cancer and ureteral involvement (HR 4.51) in the complete patient cohort.

NEW THERAPIES FOR CIS

It has been challenging to develop new intravesical therapies for CIS. There had not been a uniform definition for patients who did not respond to BCG until recently, when the definition of BCG unresponsive disease was established by Lerner et al. in 2015 as described in Table 2 [21]. Before this was established, there were problems with clinical trial design and uniformity of definitions. In addition, recently established complete response benchmarks for new therapies for BCG unresponsive CIS were developed according to AUA/FDA workshop recommendations [42–44]. A clinically meaningful initial complete response rate (for CIS) or recurrence-free rate (for papillary tumors) of at least 50% at 6 months, 30% at 12 months and 25% at 18 months is recommended, as seen in Table 3. A list of ongoing clinical trials for NMIBC BCG-unresponsive disease is shown in Table 4.

Induction and maintenance BCG is the gold standard for initial treatment of CIS [5]. The field lacks validated predictive biomarkers to identify which patients will respond to BCG therapy, largely due to multiple immune pathways involved [45]. Because of the lack of effective intravesical options, RC should be offered to patients with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or induction BCG plus maintenance [5]. Unfortunately, the last intravesical chemotherapy approved for use in BCG unresponsive disease was Valrubicin in 1998, which has a 21% complete response at 6 months but a durable 2-year response rate of only 7% [22].

New trials are evaluating the use of immunomodulators for CIS. Autenrieth et al. published a safety and efficacy assessment trial of intravesical anti-Epidermal Growth Factor Receptor antibody in BCG unresponsive patients [23]. No adverse events were noted in 12 patients and 3 of these patients were noted to be CIS free on 8 weeks follow up cystoscopy. Donin et al. recently published a 12 subject Phase 2 study using intravesical instillations of imiquimod, a Toll like receptor agonist that has been used in skin cancer [24]. The authors evaluated the safety, tolerability and activity of imiquimod in patients

Table 2
Definition of BCG-Unresponsive Disease and requirements for clinical trial enrollment [21, 44]

Definition	Requirements for BCG Unresponsive Disease
1) High grade NMIBC who have been treated with adequate BCG and are unlikely to benefit from and should not receive further intravesical BCG.	1) Patients should have received at least 2 courses of intravesical BCG – defined as at least 5 of 6 induction instillations of BCG and at least 2 of 3 instillations of maintenance BCG . Exception: those who have T1HG disease at first evaluation following induction BCG alone (at least 5 of 6 doses) would qualify.
2) These patients did not respond to BCG treatment and have a new (if previously treated for low-grade NMIBC) or persistent/recurrent high-grade recurrence between 6 (Ta/T1) and 12 (CIS) months from last BCG instillation.	2) Patients with persistent or recurrent CIS alone or with recurrent Ta/T1 disease should be within 12 months of completion of adequate BCG therapy
3) Those who despite an initial complete response to BCG, relapse with HG NMIBC within 6 months of their last intravesical treatment with BCG	3) Patients with HG papillary disease should be within 6 months of last exposure to BCG at the time of tumor recurrence – this applies especially to those on maintenance BCG. Note: for trial enrollment, they can be within 9 months (i.e. 3 months lead time for referral/enrollment is allowed). 4) No maximum limit to the amount of BCG administered, but maintenance BCG should have been administered on a schedule similar to the SWOG 8507 regimen. Single intravesical instillations do not stimulate an adequate immune response are not considered adequate maintenance therapy. 5) Patients may have CIS of the prostatic urethra at study entry. These patients require staging TURP in order to open the bladder neck for subsequent intravesical therapy and to rule out prostatic stroma involvement (T4) which would require proceeding to radical cystectomy. Patients with ductal/acinar CIS only may meet the entry criteria. 6) Note: prior to study entry, all visible papillary tumors must be resected, and if there is persistent T1HG disease on re-TUR, radical cystectomy is generally recommended. These patients should not be enrolled without a re-resection prior to study entry demonstrating less than T1 disease. 7) A patient who recurs with Ta LG may continue on therapy at the discretion of the investigator and will not be deemed to reach the recurrence endpoint in trials that require HG disease at study entry.

Table 3

Benchmark for successful intravesical therapy for BCG unresponsive-CIS [42–44]

Time after therapy has finished	Complete Response Rate
6 months	50%
12 months	30%
18 months	25%

Complete Response Rate defined as: [44]. 1) Negative cystoscopy/Negative cytology. 2) Positive cystoscopy with biopsy proven LG NMIBC and/or benign pathology/Negative cytology.

with primary, secondary or recurrent CIS. Patients with concomitant Ta/T1 that was fully resected were included. The authors evaluated the patients 6 weeks after instillation using cystoscopy and urine cytology. They found increased IL and Vascular Endothelial Growth Factor (VEGF) activity in urine specimens. Two patients did not have CIS on follow up cystoscopy. Li et al. analyzed the oncologic outcomes following intravesical Mycobacterium Phlei Cell Wall-Nucleic Acid Complex (MCNA) in patients

classified as BCG-unresponsive according to the new definition [46]. Results indicated MCNA response in the

BCG-unresponsive cohort (48.9% at 6 months, 34.8% at 1 year and 28.3% at 2 years) fell within the accepted threshold for the workshop recommendations. However, MCNA was not approved by the FDA. Dalbagni et al. published a phase II study of combination therapy with intravesical gemcitabine and oral everolimus in patients with BCG-refractory or BCG-intolerant urothelial cancer [47]. The study was terminated early due to increased toxicity and did not demonstrate a benefit compared to the use of gemcitabine alone.

In addition to immunotherapy, viral vectors have been explored for the treatment of CIS. Shore et al. performed a 43 patient, open-label, multicenter, parallel-arm, phase II study using recombinant adenovirus interferon alfa with Syn3 (rAd-IFNa/Syn3), a replication-deficient recombinant [25]. Safety and efficacy were evaluated in HG BCG refractory or

Table 4

List of current active or recruiting clinical trials evaluating therapies for BCG unresponsive NMIBC that include patients with CIS (Clinicaltrials.gov February 2019)

Trial Name	Primary Objective	Summary	Status	Sponsors
A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN)/Syn3) Administered Intravesically to Patients With High Grade, BCG Unresponsive NMIBC	To evaluate the complete response rate in patients with CIS, with or without concomitant high-grade Ta or T1 papillary disease.	This Phase III study is designed to expand the safety and efficacy of using a high dose of INSTILADRIN in patients that are “BCG Unresponsive”.	Active, Not Recruiting	FKD Therapies, Society of Urologic Oncology, Clinical Trials Consortium
Phase II Trial of Atezolizumab in BCG-Unresponsive NMIBC	To estimate complete response at 25 weeks for those with a CIS component and to evaluate event-free survival at 18 months in patients with BCG-unresponsive high-risk non-muscle invasive bladder cancer (Ta/T1/CIS) treated with atezolizumab.	This phase II trial studies how well atezolizumab works in treating patients with non-muscle invasive bladder cancer that has come back and has not responded to treatment with BCG	Recruiting	National Cancer Institute (NCI)
QUILT-3.032: A Multicenter Clinical Trial of Intravesical BCG in Combination With ALT-803 in Patients With BCG Unresponsive High Grade NMIBC	Assess incidence of complete response of CIS patients at any time.	This is a Phase II, open-label, single-arm, multicenter study of intravesical BCG plus ALT-803 in patients with BCG unresponsive HG NMIBC	Active, Recruiting	Altor BioScience
An Open Label, Single Arm, Phase II, Multicenter Study of the Safety and Efficacy of CG0070 Oncolytic Vector Regimen in Patients With NMIBC Who Have Failed BCG Therapy and Refused Cystectomy	Durable Complete Response Proportion (DCR):The proportion of patients who experience a durable complete response lasting 12 months or longer from the initial confirmed complete response date (first CR assessment to be at least 6 months after the first intravesical intervention) and at least 18 months from the date of the first intravesical intervention	To study the safety and efficacy of CG0070, an oncolytic virus expression GMCSF in HG NMIBC patients who failed BCG therapy and refused cystectomy.	Active, not recruiting	Cold Genesys, Inc.
A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of BCG-Refractory NMIBC	The number of serious adverse events associated with therapy of intravesically administered CGC [Time Frame: 6 weeks from baseline]	Phase I trial to assess the safety, toxicity, and efficacy of a novel multidrug intravesical regimen consisting of Cabazitaxel, Gemcitabine, and Cisplatin in the treatment of BCG resistant NMIBC	Active, not recruiting	Columbia University, Sanofi
A Combined Phase 1 and Phase 2 Study of Albumin-bound Rapamycin Nanoparticles (Nab-rapamycin, ABI-009) in the Treatment of BCG Refractory or Recurrent NMIBC	Number of Participants with Adverse Events as a Measure of Safety and Tolerability	Purpose of this study is to determine appropriate dosing of ABI-009 and evaluate the safety and anti-tumor activity of ABI-009 in treatment of non-muscle invasive bladder cancer	Recruiting	Aadi, LLC

(Continued)

Table 4
(Continued)

Trial Name	Primary Objective	Summary	Status	Sponsors
A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined With Intravesical BCG in Participants With BCG-Unresponsive, High-Risk, NMIBC	<ol style="list-style-type: none"> 1) Proportion of CIS participants with CR 2) Duration of complete response in CIS participants with CR 3) Event Free Survival (EFS), for all non-CIS participants 	A study to evaluate Nivolumab or Nivolumab Plus Experimental Medication BMS-986205 with or without BCG in BCG-Unresponsive NMIBC	Active, Recruiting	Bristol-Myers Squibb
A Phase 1 Dose-Escalation Study of Intravesical MK-3475 and BCG in Subjects With High Risk and BCG-Refractory NMIBC	To determine the maximum tolerated dose of the study drug (pembrolizumab [MK-3475]) when administered intravesically in combination with BCG in patients with high risk or BCG-refractory NMIBC	The purpose of this study is to evaluate the efficacy (the effect of drug on tumor) and the tolerability (the effect of drug on the body) of pembrolizumab, when given as a single agent in patients with bladder tumors. Another purpose of the study is to see what tumor characteristics are associated with increased efficacy of pembrolizumab.	Recruiting	Northwestern University
A First-in-Human Phase I Study of Intravesical sEphB4-HSA in Patients With "BCG-Unresponsive" Bladder CIS, Completely Resected High Grade Ta/T1, to Establish the Maximum Tolerated Dose (MTD) or Recommended Phase II Dose (RP2D)	<ol style="list-style-type: none"> 1) To establish the maximum tolerated dose (MTD) and recommended phase II dosing (RP2D) of intravesical sEphB4-HSA administration. 2) To describe the dose limiting toxicities and adverse event profile of intravesical sEphB4-HSA administration in patients with bladder CIS and/or high grade T1/Ta bladder cancer. 3) To describe the pharmacokinetics of intravesical sEphB4-HSA administration. 4) To explore the anti-tumor activity of intravesical sEphB4-HSA administration as manifested by responses to treatment. 	This phase I trial studies the side effects and best dose of recombinant EphB4-HSA fusion protein (sEphB4-HSA), and to see how well it works in treating participants with bladder cancer that has come back or that isn't responding to BCG	Active Not recruiting	University of Southern California
Open-Label, Multicenter, Ph 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects With NMIBC with CIS and/or High-Grade Papillary Disease of the Bladder Treated With BCG	Complete response rate in patients with CIS with or without resected papillary disease following initiation of Vicinium therapy	Because of the high risk for development of muscle invasive disease, cystectomy is recommended for CIS, high-grade Ta and T1 patients who experience disease recurrence following intravesical therapy. Vicinium is an experimental agent that may provide an alternative to cystectomy	Active, not recruiting	Viventia Bio

(Continued)

Table 4
(Continued)

Trial Name	Primary Objective	Summary	Status	Sponsors
A Phase 2 Study of BC-819 in Patients With Non-Muscle Invasive Bladder Cancer Whose Disease is Unresponsive to BCG	Complete response rate anytime on or after 12 weeks and within the first 48 weeks in patients with CIS	This study, BC-819-18-204, is a Phase 2, open-label, monotherapy, single-arm, multicenter clinical trial of BC-819 (inodiftagene vixteplasmid) in patients with NMIBC adequately treated with Bacillus Calmette-Guerin (BCG) whose disease is BCG unresponsive according to the US Food and Drug Administration (FDA) guidance	Recruiting	Anchiano Therapeutics Israel Ltd.
Mitomycin C Intravesical Chemotherapy in Conjunction With Synergo® Radiofrequency-Induced Hyperthermia for Treatment of Carcinoma <i>in Situ</i> Non-Muscle Invasive Bladder Cancer Patients Unresponsive to BCG, With or Without Papillary Tumors	Complete Response rate 3 months after study initiation	Determine whether Synergo® RITE+MMC treatment is efficacious as second-line therapy for CIS NMIBC BCG-unresponsive patients with or without papillary NMIBC, through examination of the complete response rate (CRR) and disease-free duration for complete responder	Recruiting	Medical Enterprises Ltd.
A Phase 2 Study of Check Point Inhibitor, Durvalumab (Medi4736) for BCG Refractory Urothelial CIS of the bladder	Complete Response Rate at 6 Months	Test if an experimental drug called Durvalumab (Medi4736) given by intravenous (IV) infusion is effective in treating CIS of the bladder that no longer responds to BCG and to collect information on the safety of these drugs and whether they cause any side effects.	Recruiting	H. Lee Moffitt Cancer Center and Research Institute

relapsed NMIBC patients with 35.0% of patients remaining free of HG recurrence at 12 months after the initiation of rAd-IFNa/Syn3 treatment, which was similar in the CIS only subgroup.

Radiofrequency induced chemo-hyperthermia (RF-CHT) is another possible option BCG unresponsive CIS. Van Valenberg and colleagues performed a retrospective analysis of 150 patients with CIS treated with RF-CHT [48]. These patients had a Mytomycin C 40 mg/50 mL solution instilled into the bladder followed by an intravesical microwave applicator that delivered mild hyperthermia (40.5 to 44°C) to the bladder wall. The patients were treated weekly for 4–8 weeks followed by one maintenance dose every 4–8 weeks. The BCG unresponsive cohort had a complete response (CR) rate of 46% at 6 months, in line with the AUA/FDA recommendations. The bladder preservation rate for

this cohort was 71% at 45 months. On the other hand, Tan and colleagues found worse DFS when comparing RF-CHT to a second course of BCG induction and subsequent maintenance (HR 2.06, 95% CI 1.17–3.62, $p=0.01$) in patients with BCG recurrence following induction or maintenance BCG [49].

New chemotherapy combinations have been explored for treatment of BCG unresponsive NMIBC. Steinberg et al. performed a retrospective review of 45 patients treated with induction intravesical Gemcitabine/Docetaxel that consisted of weekly administration for 6 weeks [26]. This was followed by monthly maintenance instillations if the patients did not have disease on initial surveillance. Of the total patient cohort, 91% were BCG refractory, relapsing or intolerant and 64% had CIS on pathology. The authors defined treatment success as no bladder

cancer recurrence and no cystectomy. Results demonstrated 66% success at first surveillance, 54% at 1 year and 34% at 2 years, which are higher than the meaningful clinical response rates proposed by the AUA/FDA workshop [42–44]. Of those patients who ended up requiring cystectomy, all had negative surgical margins and lymph nodes. Milbar and colleagues [27] performed a retrospective study of 33 patients using the same Gemcitabine/Docetaxel regimen as Steinberg et al. [26]. BCG unresponsive/relapsing disease was present in 76% of the cohort with 56% of these patients having CIS. These patients had 49% 1-year High Grade-Recurrence Free Survival (HG-RFS), 34% 2-year HG-RFS with a median HG-RFS of 6.5 months.

CONCLUSION

There have been remarkable discoveries with regards to the biology of CIS. Advancements in immunobiology and molecular genetics have enabled better understanding of this disease. New developments in diagnostics have enabled effective detection of CIS. Large studies have also contributed to an understanding of the effect of CIS on cancer related outcomes. Some intravesical therapies show promise in treating BCG unresponsive CIS. Unfortunately, these therapies have not been FDA approved and are still in the clinical trial phase. The establishment of a BCG-unresponsive definition coupled with discoveries in tumor biology will enable discovery of more effective treatments.

Key Points

- Hedegaard and colleagues studied the genetics of bladder cancer and divided it in three groups based on molecular profile. CIS was associated to the most aggressive molecular subtype. Dyrskjöt and colleagues examined gene expression patterns in NMIBC with surrounding CIS, without surrounding CIS, and in MIBC.
- Photodynamic Diagnosis and Narrow Band Imaging have been showed to be more effective than White Light in detecting CIS.
- CIS has been associated to decreased pathological response after Neoadjuvant Chemotherapy. It has been associated to increased cancer recurrence and mortality in pT0-T2 disease.
- Clinical Trials are evaluating new therapies for BCG unresponsive CIS. Some of these

include the use of immunomodulators, intravesical chemotherapy and viral vectors. The last FDA approved intravesical therapy was valrubicin in 1998.

CONFLICT OF INTEREST

J. R. Mirabal has not conflict of interest to report.

S. P. Lerner: Clinical trials – Endo, FKD, JBL (SWOG), Roche/Genentech (SWOG), Urogen, Vaxion, Viventia; Consultant/Advisory Board – Archiano Therapeutics, Ferring, Merck, QED, Roche/Genentech, UroGen, Vaxiion, Verity; Speaker honoraria – Nucleix, Dava Oncology; Patent – TCGA classifier

J. A. Taylor: Clinical Trial – Bionovus/Ciclomed; Consultant/Advisory Board – Photocure, BMS; Faculty/Speaker – ASCO

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