Emerging intravesical therapies for the management of bacillus Calmette–Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer: Charting a path forward

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Abstract

Management of patients with cacillus Calmette–Guérin (BCG)-unresponsive, high-risk, non-muscle-invasive bladder cancer (NMIBC) presents a formidable clinical challenge that requires urologists to weigh the competing risks of progression during further intravesical therapy vs. the morbidity of radical cystectomy. The prognosis of high-risk NMIBC recurring after BCG depends on the adequacy of prior BCG, the timing of recurrence, and tumor histology. The standard of care is currently radical cystectomy, as effective salvage intravesical therapy has not been established. The development of bladder-sparing treatments has been hampered to date by inconsistent definitions of BCG failure and difficulties in identifying appropriate control treatments in clinical trials. Despite these limitations, the spectrum of salvage therapy is expanding to include enhanced intravesical chemo-, gene, and immuno-therapies. In this review, we provide an overview of these emerging agents in the context of our current understanding of BCG failure and the unique considerations for clinical trial design in this disease state.

Introduction

Bladder cancer is the fifth most commonly diagnosed malignancy and is responsible for approximately 20,000 deaths per year in Canada and the United States.[1,2,3] The majority (≈75%) of tumours are non-muscle invasive. Standard therapies of non-muscle invasive bladder cancer (NMIBC) include transurethral bladder tumour resection (TURBT) and intravesical therapy with chemotherapy or Bacillus Calmette–Guérin (BCG). Despite optimal therapy, up to 80% of tumours recur, and anywhere from 0-40% progress to muscle-invasive disease, depending on risk factors.[4] The treatment options especially for high grade NMIBC that has recurred despite optimal BCG therapy are limited. There are no established second-line salvage intravesical therapies, and the standard of care for these patients is radical cystectomy. The management of high grade NMIBC recurring on or after BCG therapy represents a critical unmet need in Urology. In this narrative review we aim to demonstrate the gaps in current standard management of NMIBC, and to review the novel therapies on the horizon to address these gaps.

Optimal risk-adapted therapy for non-muscle-invasive bladder cancer

NMIBC is stratified into low-, intermediate-, and high-risk disease states based on risk of recurrence and progression. The most important risk factors are T-stage, tumour grade, presence of carcinoma in situ (CIS), tumour size, multifocality, and prior history of recurrence (Table 1).[5,6] Low and intermediate risk tumours are generally effectively managed with TURBT and judicious use of intravesical therapy.[7] These may recur in a high proportion of cases (40-60%). The risk of progression to higher stage disease is rare for low-risk disease, but ranges from 5-15% for intermediate risk disease.[8] In contrast, high-risk patients are at increased risk of progression, measuring approximately 50% over 15 years in one series.[4,9] Standard of care for high-risk disease is intravesical immunotherapy with BCG. BCG is believed to augment the anti-tumour immune response by promoting T-cell recruitment, cytotoxic activity, and cytokine release.[10] A Cochrane review on intermediate- and high-risk NMIBC demonstrated that BCG reduced the odds of disease progression by 56% compared to TURBT alone.[11] BCG has also been shown to be superior to mitomycin C (MMC) in reducing recurrence (OR 0.56)[12]. The direct comparison to MMC with respect to progression is less clear[13,14], but only BCG with maintenance has been shown to reduce progression in an individual trial[15]. Optimal BCG is delivered as a weekly induction for 6 weeks followed by 3 weekly maintenance instillations at 3, 6, 12, 18, 24, 30 and 36 months, as per prior randomized controlled trials (RCTs) which demonstrate superior oncological outcomes this maintenance protocol.[15,16]

Defining recurrence after BCG

Unfortunately, BCG will fail in 30-40% of patients with NMIBC.[17] High-grade recurrence after BCG presents a challenging scenario and the evidence for optimal treatment of these patients is difficult to interpret because of varied definitions of BCG failure. Technically, a BCG failure can be taken to represent any recurrence during or after BCG therapy. However, several factors help to stratify BCG failure, including the timing of recurrence and the adequacy of prior BCG. BCG failure is often stratified into BCG-relapsing, -refractory, and -unresponsive disease, assuming adequate BCG induction and maintenance[18] (Figure 1). BCG relapsing disease can be heterogenous depending on the time to relapse. An early relapse has a similar outcome to BCG refractory disease, but late relapses may respond to additional BCG[19] and generally have a more favorable outcome.[20,21] An early relapse is defined as recurrence within 6 months of the last BCG dose for papillary (Ta/T1) NMIBC and within 12 months for CIS.[21] BCG-refractory NMIBC is defined as high-grade recurrence or failure to eradicate disease with induction and the first cycle of maintenance BCG (or second induction cycle) if the recurrence is CIS or high grade Ta disease. If the recurrence is a high grade T1 tumour, it is considered BCG-refractory after induction BCG alone. Any patient with BCG-refractory NMIBC or an early relapse is termed to be BCG-unresponsive. This is an important definition for both clinical practice and clinical trial design, as it delineates a group of patients who are unlikely to benefit from additional BCG.

The natural history of BCG refractory disease is often progression to muscle-invasive cancer, metastasis, and even death.[9,22] It is essential to re-evaluate the upper tract and prostatic urethra in patients with suspected recurrence after BCG since approximately 50% of patients will harbour disease in these locations.[23] Historical data suggest that the risk of metastasis in patients with BCG failure reaches 50% after 3 additional cycles of BCG.[24] Complete response rates to a second course of BCG range from 20%-50%[25] depending on the category of BCG failure, tumour histology, and presence of CIS, which is associated with 50% progression.[26] Early radical cystectomy provides the best oncologic outcomes with a disease-free rate greater than 90%.[27] All forms of salvage intravesical therapy for both BCG refractory and relapsing disease must be considered oncologically inferior to cystectomy.[6]

Salvage intravesical therapy in North America often consists of BCG/interferon-alpha (BCG/IFN). The evidence in support of this regimen comes from a large prospective trial of over 400 BCG naïve and failure patients (including both refractory and relapsing disease), which showed cancer-free rates at 2 years of 59% and 45%, respectively, when treated with BCG/IFN.[28] A subsequent re-analysis showed that response to BCG/IFN was strongly associated with the category of BCG failure[29]. To illustrate, BCG refractory

patients had only 34% recurrence-free survival compared to 53% for patients relapsing within 12-24 months. The largest limitation is that there is no data directly comparing BCG/IFN to BCG monotherapy, which is regarded as an appropriate therapy in the late BCG-relapsing disease space.

Emerging chemotherapeutic agents

The use of intravesical chemotherapeutic agents such as gemcitabine, valrubicin, epirubicin and docetaxel as salvage therapy for BCG failure has been under investigation for at least 20 years (Table 2). Of these, only valrubicin is currently Food and Drug Administration (FDA) approved for management of BCG-refractory CIS based on a phase 2 multicentre single-arm trial which demonstrated a 21% complete-response rate in patients with recurrent CIS.[30] This translated to an 8% disease-free rate at 30 months, which would likely be inadequate for FDA approval currently. While it is the only FDA approved drug in this setting, and although there are currently no other established standard salvage therapies for BCG-unresponsive disease, valrubicin is not necessarily most commonly used. Intravesical gemcitabine represents a reasonable option based on trial data and its known efficacy when administered systemically for muscle invasive and metastatic urothelial carcinoma. Gemcitabine was shown to be superior to MMC in a head-to-head RCT for BCG failure.[31] Another RCT comparing repeat BCG to intravesical gemcitabine showed that the latter significantly improved recurrence-free survival (19% vs. 3%), although it did not impact disease progression.[32] Barlow and colleagues treated 54 NMIBC (87% high-risk) BCG non-responders with intravesical docetaxel induction and maintenance with a 25% recurrence-free survival at 3 years and 85% disease-specific survival at 5 years.[33] Combination therapy has also been tested with encouraging results.[34]

A key short-coming in these trials is that they were conducted prior to our current understanding of optimal BCG, the importance of maintenance BCG, and risk-stratifying BCG failures. These considerations were also not reflected in older NMIBC guidelines.[35] Therefore, the inclusion criteria for these studies did not control for the dose/duration of BCG and time from completion of BCG to recurrence. BCG intolerant patients were also commonly combined with refractory/relapsing patients, and some studies included intermediate risk patients. Lastly, since these are mostly single-arm efficacy trials without a control group we cannot conclude whether the above treatments are superior to repeat BCG. Despite these limitations, there is little disagreement within the urologic community that the outcomes of salvage intravesical chemotherapy in patients recurring after BCG are sub-optimal. We can cautiously conclude that approximately 70-80% will have a recurrence within 2 years after starting salvage chemotherapy.

Clinical trial design and BCG failure

Given the limited utility of salvage intravesical chemotherapy in the management of BCG failure, there is a large unmet need for novel bladder-sparing therapies. Indeed, since 1959 there have only been 2 new treatments approved by the FDA (valrubicin and thiotepa), neither of which has demonstrated robust anti-tumour response. Much of the limited development in NMIBC therapeutics stems from ethical and logistical questions that form the backbone of designing meaningful clinical trials for BCG failure:

1. How do we define BCG failure when recruiting patients for clinical trials?
2. How do we appropriately combine patients who have CIS vs. high-grade papillary recurrence on BCG?
3. What is the most appropriate control group when comparing a novel therapy (e.g. cystectomy vs. repeat BCG vs. investigator's choice salvage therapy)?
4. Is it safe to delay cystectomy in operative candidates to evaluate a novel intravesical therapy?
5. What is the most clinically relevant outcome when weighing competing co-morbidities in the NMIBC population (e.g. overall survival, disease-specific survival, response rates, recurrence)?

The FDA held a special meeting in 2013 in conjunction with representatives from the American Urological Association to discuss these implications and to improve consensus on clinical trial design in BCG failure.[36] This collaboration triggered the subsequent evolution of the term "BCG-unresponsive"[37, 38] and finally a guidance document from the FDA for conducting clinical trials in this disease space.[39] A key objective of these initiatives was to define stringent inclusion criteria for clinical trials that would eliminate some of the patient heterogeneity encountered in prior studies.

Contributing to the heterogeneity of the NMIBC population are the differences in natural history and management of CIS compared to papillary tumours (Ta/T1). Patients with CIS are presumed to have residual disease at the time of starting intravesical therapy, while patients with papillary tumours have undergone complete resection of their disease. Disease eradication with novel therapies can therefore only be demonstrated in patients with CIS. As a result, the FDA typically requires that the primary endpoint of registration trials in the BCG-unresponsive disease state be the complete response (CR) rate in patients with CIS (with or without concomitant papillary tumour). Patients with papillary tumors only are still included in the trials, and high-grade recurrence-free survival of these patients usually constitutes a co-primary or secondary endpoint of the trial. The FDA has suggested that an investigational agent should demonstrate a CR rate of 40-50% at 6 months for BCG-refractory CIS and a recurrence free-survival rate for Tis/Ta/T1 tumors of 30% at 18-24 months with the lower limit of the 95% confidence

interval excluding 20%. These numbers have been criticized for being unrealistic and some worry it will further deter drug development in an already challenging disease state.[40] It remains to be seen if the FDA will approve a novel therapy for both CIS and Ta/T1 patients based on this type of trial design, as the final approval decision will always be dependent on panel review of clinical trial results for the individual agent.

The FDA accepts single arm phase 2 trials for registration of novel therapies in patients with BCG-unresponsive NMIBC because there is consensus in the field that there is no appropriate control group to which to compare.[39] A placebo or further BCG would be considered unethical. One could consider randomization to radical cystectomy, but the feasibility of such a trial would be low. If a new agent is approved in the near future, standard clinical trial design could evolve to include randomization to the newly approved agent.

Another important question is whether cystectomy can be safely delayed to evaluate a novel therapy. Retrospective studies have shown that cystectomy can be delayed up to 1 year after initial TURBT in high-risk BCG-refractory urothelial carcinoma with no effect on disease-specific mortality.[41] Furthermore, prospective studies following the natural history of BCG treatment demonstrated that progression rarely occurs at 6 months and the median time to progression of T1HG disease is approximately 24 months.[42] Furthermore, the recently presented preliminary data from the Keynote 057 trial showed that none of 102 patients with BCG-unresponsive CIS progressed during a median of 15.8 months of follow-up.[43]

Novel therapies

Therapies currently being investigated for BCG failure are summarized in Table 3, with certain examples highlighted in the text below.

Enhanced intravesical chemotherapy

Device-assisted chemotherapy aims to improve the penetration of the drug through the urothelium using heat (chemohyperthermia; CHT) or electrical current (electromotive drug administration). Of the two, chemohyperthermia has been studied more extensively in the setting of BCG failure.[44,45,46] The Synergo system (radiofrequency-induced thermo-chemotherapy (RITE)) uses a catheter with microwave applicator at the tip that heats MMC in the bladder to 41-44°C. Data on CHT are largely heterogeneous with recurrence-free survival ranging from 25-50%.[44] Arends and colleagues[47] collected prospective data on high- and intermediate-risk NMIBC (81% had prior BCG) treated with MMC or epirubicin with CHT and report a 2-year recurrence-free survival of approximately 50% for both agents. The recently reported HYMN trial randomized 104 intermediate or high risk patients after BCG failure to either RITE or “institutional

standard second-line therapy" (i.e. electromotive mitomycin, repeat BCG, or conventional mitomycin).[48] There was no difference in disease-free survival or 3 month CR rate in CIS patients. This trial, however, has been criticized for design concerns, especially the heterogeneity of the patient population, and the details of drug delivery, especially the dose of mitomycin delivered.[49] Van Valenberg and colleagues retrospectively examined the outcomes of patients with CIS +/- papillary NMIBC receiving Synergo.[50] Amongst patients with a complete response at 6 months, recurrence-free rates were 17% for BCG-unresponsive and 27.3% in other categories of BCG failure. However, only half of patients with BCG-unresponsive disease and 70% of other failures were able to achieve CR.

Another early concept is the use of standard intravesical chemotherapy agents incorporated into micelles. These nanoparticles are believed to act as mucoadhesives, improving the attachment of cytotoxic agents to the urothelium, increasing dwell time, and enhancing drug uptake.[51] A single-arm phase 2 trial testing albumin-bound paclitaxel in 28 high-risk NMIBC patients with recurrence after BCG induction (i.e. not true BCG-unresponsive NMIBNC) demonstrated recurrence-free survival of 18% and cancer-specific survival of 91% at a median follow-up of 41 months.[52] It is not clear that these results are any better than would be anticipated with un-encapsulated docetaxel. A clinical trial investigating intravesical hyperconjugated polyglycerol-encapulsated docetaxel is under way.[53]

Photodynamic therapy

Photodynamic therapy uses light energy to eradicate malignant urothelial cells. Systems currently being investigated first require intravesical instillation of a photosensitizing agent followed by insertion of a urinary catheter capable of transmitting light from an external source. Bader *et al.*[54] tested photodynamic therapy with hexaminolevulinate in a small series of 17 patients with recurrent NMIBC. While the majority had high-grade disease, only 12 had prior BCG therapy with no data on adequacy or nature of recurrence. Twelve percent of patients were tumour-free at 21 months. A Phase I study investigating a different photosensitizer (TLD1433) has been completed[49] and a larger phase II trial in the BCG-unresponsive setting is planned.[50]

Immunotherapy

Inhibitors of programmed cell death protein (PD1) and PD1 ligand (PDL1), (collectively termed immune checkpoint inhibitors) represent a major breakthrough in the treatment of patients with metastatic bladder cancer. These agents interrupt a negative regulatory signal that suppresses tumor cell kill by activated T-cells, thereby triggering an anti-tumour response.[57,58] Two registration trials are testing the efficacy of checkpoint

inhibitors in BCG-unresponsive NMIBC.[43,59] Keynote 057 reported preliminary results at the annual meeting of the European Society of Medical Oncology in October 2018. The 3-month CR rate in 102 patients with BCG-unresponsive CIS was 40.2%.[43] These therapies would represent a potential paradigm change for the management of patients with NMIBC since they are systemic therapies usually administered by medical oncologists in North America.

Gene therapy

Gene therapy is one of the most active areas of translational research for bladder cancer, and three promising agents are in advanced stages of clinical development.

Adstiladrin® (rebranded from Instiladrin®; nadofaragene firadenovec) is a replication-deficient adenovirus programmed to express interferon-alpha, that is administered together with an incipient Syn3 to promote update of the virus into tumour tissue. This agent has passed through phase I and II trials and is now being tested in a second large single arm trial (phase III). Of 40 patients with BCG-unresponsive NMIBC in the phase II trial, 14 (35%) were free of high grade recurrence at 12 months.[60] The phase III trial is an FDA registration trial.[61]

CG007 is a conditionally replicating oncolytic adenovirus that expresses granulocyte-monocyte colony stimulating factor (GM-CSF). Viral replication and GM-CSF expression are directly and indirectly under the control of the E2F-1 promoter,[62] which is active only in cancer cells with loss of retinoblastoma (Rb). This provides tumor selectivity. After a successful phase I study that demonstrated safety and an early signal for efficacy,[63] CG0070 was tested in a single arm phase II trial in patients with BCG-unresponsive NMIBC.[64] The agent was administered weekly for a 6 week induction course, followed by maintenance dosing at 6, 12, and 18 months. Interim results from 45 patients revealed a 47% CR rate at 6 months. In a subsequent update[65] of these trial results in a meeting presentation, the CR rate at 12 months in 61 patients was 30% (27% in CIS and 38% in pure Ta/T1). Ten patients underwent cystectomy, of whom 6 had MIBC. Most of the adverse events related to lower urinary tract symptoms, in addition to flu-like symptoms and fatigue. Final results of this trial will determine if it can move towards FDA approval and clinical implementation.

BC-819 is a plasmid administered intravesically with polyethyleneimine, a cationic membrane permeabilizer.[66] The plasmid encodes the diphtheria toxin under the control of the H19 promoter sequence, an oncofetal transcription factor upregulated in urothelial carcinoma. Selective synthesis of diphtheria toxin in tumour cells causes arrest of protein synthesis and subsequent cell death without compromising the benign urothelium. A phase 2 marker lesion trial was completed in 2013[67] for patients with intermediate-risk disease only (no high grade or CIS) who had recurrent or persistent disease after at least 1

course of any intravesical therapy. The authors report that BC-819 eradicated one-third of all marker lesions and 40% of patients remained disease-free at 2 years. A trial testing BC-819 in BCG-unresponsive NMIBC has not yet launched.[68]

Targeted therapy

Vicinium (oportuzumap monatox; VB4-845) is a recombinant protein comprised of a single chain variable fragment of a humanized anti-EpCAM antibody fused to Pseudomonas exotoxin A.[69] Its tumour specificity rests on increased plasma membrane expression of the EpCAM surface marker on urothelial carcinoma.[70] Binding of the anti-EpCAM component to EpCAM causes internalization of the Pseudomonas exotoxin by receptor-mediated endocytosis, and the toxin causes arrest of protein synthesis. Vicinium is therefore only efficacious against tumours expressing EpCAM, which has been a consistent inclusion criterium for enrolment in clinical trials.

In a phase 2 study with EpCAM-expressing CIS, most of which was BCG refractory, 40% of patients obtained a CR and 16% remained disease-free at 18-25 month follow-up[71]. Interim results from a single arm phase III FDA registration trial in patients with BCG-unresponsive NMIBC were reported at the 2018 meeting of the AUA.[72] Vicinium was instilled into the bladder two times per week for 6 weeks followed by weekly for 6 weeks and every 2 weeks for up to 2 years. The CR rate at 3 months in CIS patients was 42%. The 12 month results of this trial are expected in mid 2019. There is also a phase III trial testing Vicinum in combination with the checkpoint inhibitor durvalumab (NCT03258593).[73]

Conclusions

The landscape of clinical trials in BCG failure has shifted dramatically from intravesical chemotherapy to novel gene, immune, and targeted therapies with more consistent standards for patient selection and outcome reporting. Most studies remain single-arm trials due to the lack of a defined control to which to compare. Since the BCG-unresponsive patient population is still quite heterogenous, it is impossible to compare drugs across trials. Encouraging early results have been reported for several agents, including especially Vicinium, Adstiladrin®, GC0070 and Pembrolizumab, so that any one or more of these agents could obtain FDA approval in the US in the near future. Once one or more agent is available in clinical practice, the clinical trial space will need to evolve to encompass comparison trials to the newly established effective agents. If multiple agents are approved, we will need to investigate whether there are markers to guide the use of one therapy over another, and to guide the best sequence of therapies. Combination therapies will be an important future area of clinical trial investigation.

Furthermore, it remains to be seen how systemic delivery of a checkpoint inhibitor will be accepted in this patient population, especially if intravesical alternatives are available.

It is important to bear in mind that these therapies are being tested in patients who are ineligible for or decline cystectomy for BCG-unresponsive NMIBC. Many patients ultimately chose clinical trial participation over cystectomy, and some proceed to cystectomy if the trial agent does not work. With one or more effective, FDA-approved salvage therapy options for patients with BCG-unresponsive NMIBC it will be even more important to identify in which patients it is safe to delay cystectomy.

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Figures and Tables

Fig. 1. Overview of standard of care for bladder cancer. *All evaluations should comprise of cystoscopy, urine cytology, and random bladder biopsies for CIS. Papillary disease at 3 months requires resection. Any recurrence while on BCG with muscle-invasive disease is managed according to the MIBC pathway. BCG bacillus Calmette Guerin; CIS: carcinoma in situ; MIBC: muscle invasive bladder cancer; NMIBC: non-muscle-invasive bladder cancer.

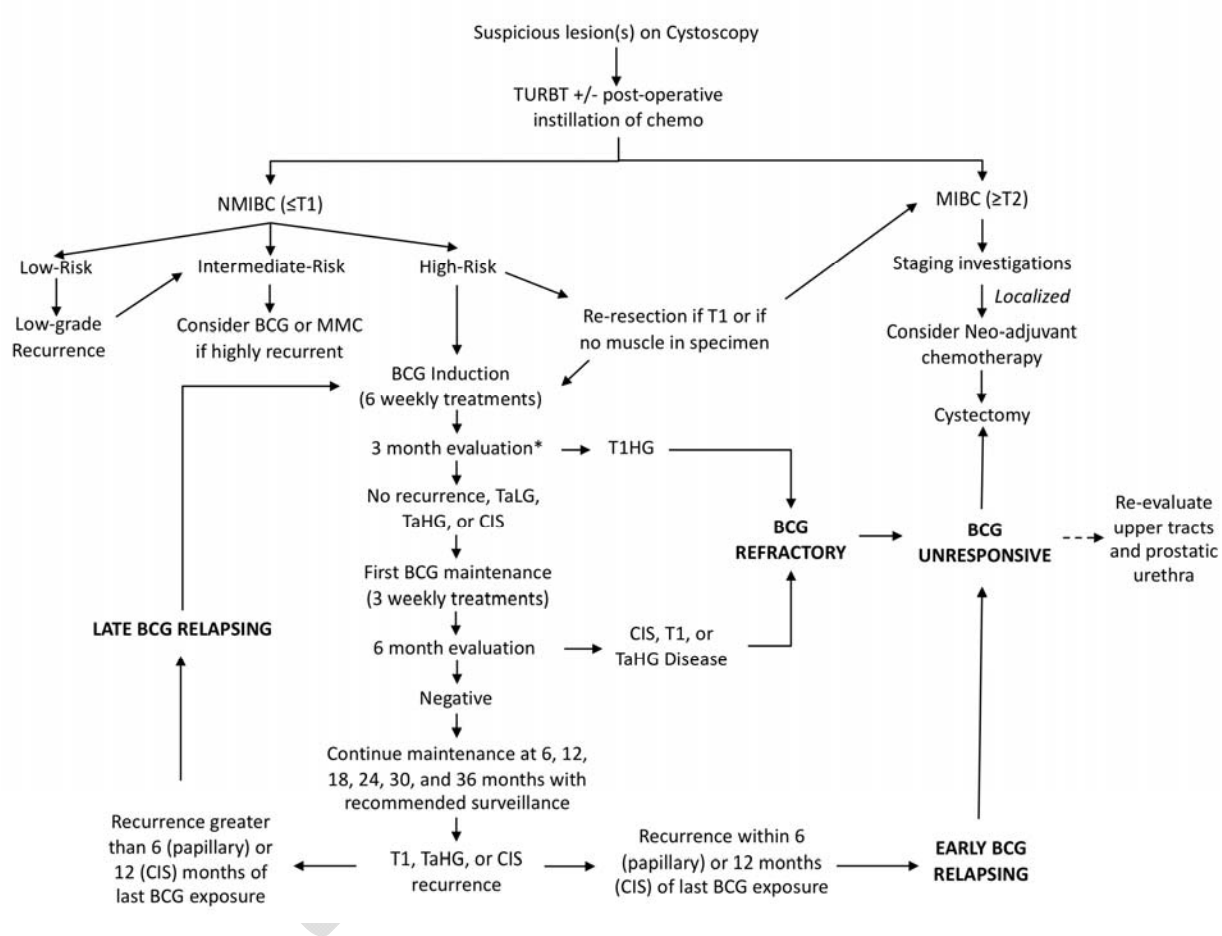

Table 1. Risk stratification for NMIBC (2016 AUA guidelines)		
Low-risk	**Intermediate-risk**	**High-risk**
Low-grade solitary Ta ≤ 3 cm	Recurrence with 1-year low-grade Ta	High-grade T1
Papillary neoplasm of low malignant potential	Solitary low-grade Ta >3 cm	Any recurrent, high-grade Ta
	Low-grade Ta, multifocal	High-grade Ta, >3 cm (or multifocal)
	High-grade Ta, ≤3 cm*	Any CIS
	Low-grade T1*	Any BCG failure in high-grade case
		Any variant histology
		Any LVI
		Any high-grade prostatic urethral involvement

*EUA and CUA guidelines for non-muscle-invasive bladder cancer classify these tumors has high-risk. The downgrading of these tumors to intermediate-risk by the AUA was based on the lack of BCG maintenance in studies assessing progression and how the panel felt these tumors would behave with adequate BCG. AUA: American Urological Association; BCG bacillus Calmette Guerin; CIS: carcinoma in situ; CUA: Canadian Urological Association; EAU: European Association of Urology; LVI: lymphovascular invasion; NMIBC: non-muscle-invasive bladder cancer.

Table 2. Key trials for chemotherapy in BCG failures				
Agent	**Study**	**Study design**	**Inclusion criteria**	**Outcome**
Valrubicin	Steinberg et al[1]	Phase 2, single-arm trial	1. Any failure or recurrence after 6-week induction BCG for CIS 2. BCG intolerant	– 20% complete response – 8% disease-free at 30 months – 50% required cystectomy
Gemcitabine	Adeo et al[2]	RCT of intravesical gemcitabine vs. MMC	1. Any recurrence or progression after BCG of unspecified dose/duration. 2. BCG ineligible patients	– 72% of gemcitabine and 61% of MMC patients free of disease at median of 36 months
Gemcitabine	Dalbagni et al[3]	Phase 2, single-arm trial	1. Disease that was deemed refractory to BCG of unspecified dose/duration 2. BCG intolerance	– 39% complete response – 21% disease-free at 1 year
Gemcitabine	Di Lorenzo et al[4]	RCT of intravesical gemcitabine vs. repeat BCG	1. Patients failing BCG as per EAU 2008 guidelines (do not account for dose/duration of BCG or BCG refractory vs. relapsing disease)	– 19% of gemcitabine and 3% of repeat BCG patient free of disease at 2 years – ~35% progression for both groups

[1]Steinberg G, Bahnson R, Brosman S, et al. 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;163:761-7. [2]Adeo R, Caraglia M, Bellini S, et al. Randomized, phase 3 trial on gemcitabine vs. mytomicin in recurrent superficial bladder cancer: Evaluation of efficacy and tolerance. *J Clin Oncol* 2010;28:543-8. [3]Dalbagni G, Russo P, Ben-Porat L, et al. Phase 2 trial of intravesical gemcitabine in bacille Calmette-Guérin-refractory transitional cell carcinoma of the bladder. *J Clin Oncol* 2006;24:2729-34. [4]Di Lorenzo G, Perdonà S, Damiano R, et al. Gemcitabine vs. bacille Calmette-

Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: A multicenter, prospective, randomized trial. *Cancer* 2010:116:1893-900. BCG bacillus Calmette Guerin; CIS: carcinoma in situ; EAU: European Association of Urology; LVI: lymphovascular invasion; MMC: mitomycin C; NMIBC: non-muscle-invasive bladder cancer; RCT: randomized control trial.

Table 3. Ongoing clinical trials investigating novel agents in BCG failure

Agent	Study	Study design	Inclusion criteria	Mechanism	Primary outcomes
Enhanced intravesical chemotherapies					
Synergo	NCT02471495	Phase 3, single-arm trial	Persistent CIS after induction plus maintenance BCG at 6 months, recurrent disease within 3 months of starting BCG, or disease progression	Microwave-emitting catheter to improve penetrance of MMC	Recurrence-free survival
Nanoxel	NCT02982395 [47]	Phase 3, double-arm, open-label study comparing nanoxel to mitomycin C	Any NMIBC "unresponsive" to BCG	Paclitaxel-containing micelles (nanoparticles)	Recurrence-free survival
Nab-Rapamycin (ABI-009)	NCT02009332	Combined phase 1 and 2, single-arm study	Phase 2: high-grade NMIBC BCG refractory[1] or relapsing <6 months despite adequate BCG	Rapamycin-containing micelles (nanoparticles)	Adverse events
Intravesical Cabazitaxel, Gemcitabine, and Cisplatin	NCT02202772	Phase 1, single-arm	High-grade NMIBC with persistent or recurrent disease after BCG induction	Combination intravesical chemotherapy	Safety and tolerability

Photodynamic therapy	NCT03053635	Phase 1, single-arm	Any NMIBC with persistent tumor after adequate BCG or BCG intolerant	Instillation of photosensitizer (TLD1433) followed by transurethral irrradiation	Safety and tolerability
Immunotherapy					
Durvalumab	NCT03317158	Multi-arm, phase 1/2 study comparing durvalumab ± BCG ± EBRT	Any-grade recurrent NMIBC despite adequate BCG	PD-1 inhibitor, enhancing T-cell mediated anti-tumor activity	Phase 1: Determine recommended combination doses Phase 2: 6-month relapse-free survival (RFS)
	NCT02901548	Phase 2, single-arm, open-label	BCG refractory or relapsing <9 months CIS only		CR rate
Pembrolizumab	NCT02808143	Phase 1, dose-escalation	High-grade NMIBC BCG refractory or relapsing <6 months despite adequate BCG.		Maximum tolerated dose of pembrolizumab
	NCT02625961	Phase 2, single-arm, open-label	High-risk NMIBC unresponsive to adequate BCG (undefined)		CR rate Disease-free survival rate
Atezolizumab	NCT02844816 [50]	Phase 2, single-arm, open-label	High-grade NMIBC BCG refractory or relapsing <6 months	PD-L1 inhibitor, enhancing T-cell mediated anti-tumour activity	CR rate Event-free survival
	NCT02792192	Phase 2, multi-arm trial comparing atezolizumab ± BCG stratified by BCG-unresponsive	Any BCG-refractory or -relapsing NMIBC with CIS		Adverse events Maximum tolerated dose of BCG in combination with atezolizumab CR rate

		and relapsing disease			
ALT-801	NCT01625260	Phase 1b/2, single-arm trial of combination intravenous ALT-801 and intravesical gemcitabine	Any high-grade NMIBC, multi-focal disease, or tumour >4 cm. BCG intolerant or recurrent disease after 1 course of BCG	Recombinant IL-2-T-cell receptor domain fusion protein. Potent IL-2 receptor agonist	Adverse events CR rate
PANVAC Vaccine	NCT02015104	Phase 2, RCT of BCG alone vs. BCG + PANVAC	Any high-grade NMIBC recurring after at least 1 induction course of BCG	Subcutaneous vaccine composed of viral vectors encoding common tumor antigens	Improved disease-free survival in PANVAC + BCG group
Recombinant intravesical therapies					
rAd-IFNα/Syn3	NCT01687244	Phase 2, RCT comparing 2 doses	High-grade BCG relapsing or refractory NMIBC	Interferon-α expressing adenovirus	35% of patients free of high-grade disease at 12 months
	NCT02773849	Phase 3, single-arm, open label	High-grade NMIBC BCG relapsing <12 months		CR rate in patients with CIS
Vicinium	Kowalski et al[65]	Phase 2, non-randomized, open-label trial comparing 6- vs. 12-week induction	High-grade NMIBC failing to respond to ≥1 cycle of BCG or BCG-intolerant	Pseudomonas exotoxin-anti-EpCAM fusion protein	~ 40% CR in both groups at 3 months
	NCT02449239	Phase 3, single-arm	High-grade NMIBC with any recurrence/persistence despite adequate BCG		CR rate
CG0070 oncolytic virus	NCT02365818	Phase 2, single-arm trial	Any high-grade NMIBC that is BCG refractory or	GMCSF-expressing oncolytic virus	% with CR >12 months

			relapsing up to 24 months from last BCG exposure		
Other therapies					
Sunitinib	NCT01118351	Phase 2, single-arm open label	Any recurrent NMIBC following BCG treatment	Tyrosine kinase inhibitor	CR rate
Vicinium + Durvalumab	NCT03258593	Phase 1, single-arm	High-grade NMIBC BCG refractory or relapsin	See above	Safety and tolerability

[1]The concepts BCG refractory, BCG relapsing, and adequate BCG are consistent with the definitions outlined in the text. BCG bacillus Calmette Guerin; CIS: carcinoma in situ; CR: complete response; MMC: mitomycin C; NMIBC: non-muscle-invasive bladder cancer; RCT: randomized control trial.