Review article

Theories behind Bacillus Calmette-Guérin failure in high-risk non-muscle-invasive bladder cancer and update on current management

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HIGHLIGHTS

- High-risk non-muscle invasive bladder cancer (NMIBC) represents a heterogeneous group with differing outcomes. The gold standard treatment for these patients is the intravesical installation of Bacillus Calmette-Guérin (BCG).
- BCG upregulates cytokine activity and T cell differentiation to induce cytotoxicity and phagocytosis in bladder cancer cells.
- The definition of BCG-resistant bladder cancer may vary depending on different guidelines.
- Research on new therapies for BCG-resistant non-muscle-invasive diseases is required.

GRAPHICAL ABSTRACT
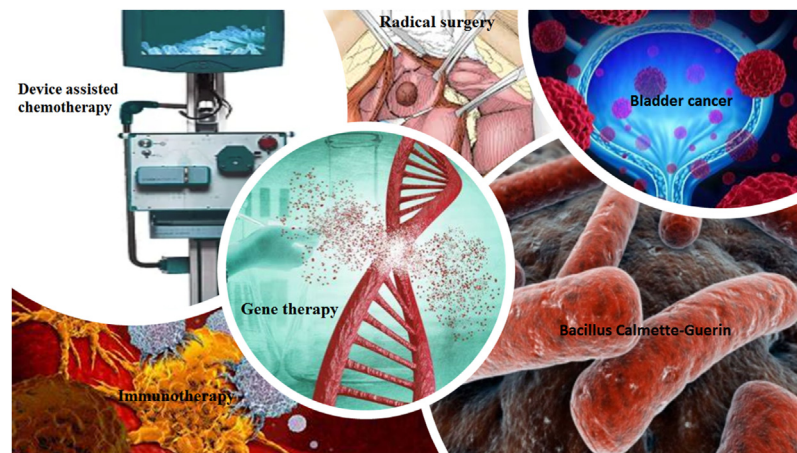
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ABSTRACT

Bladder cancer encapsulates a wide spectrum of disease severities, with non-muscle invasive bladder cancer (NMIBC) representing an entirely different entity from muscle-invasive disease. Bacillus Calmette-Guérin (BCG) is one of the most successful intravesical treatment methods for patients diagnosed. However, a considerable proportion of patients fail to respond to BCG treatment. Given the propensity for recurrence in patients with high-risk bladder cancer, these patients present with surgical dilemmas. There is currently no gold standard for salvage treatment post-BCG failure or unified definition as to what that means. In this review, we discuss the mechanisms of action and pathophysiology of BCG, potential theories behind BCG failure, and the scope of novel treatments for this surgical conundrum.

Introduction

Bladder cancer imposes a significant global health burden. In 2020, approximately 570,000 new cases were diagnosed, making it the sixth most common cancer in men and the 10th most common cancer, globally.[1] This complex and heterogeneous disease ranges from solitary, non-invasive low-grade tumors that can be cured with surgical excision as a day-case endoscopic procedure to muscle-invasive disease with a

high risk of metastatic disease despite chemotherapy and radical treatment with a poor prognosis of 50 % survival in 5 years.

Of patients diagnosed with bladder cancer, 75 % present with superficial disease, namely, non-muscle invasive bladder cancer.[2] Although NMIBC is often associated with favorable outcomes, further subclassification into high- and low-risk diseases can assist in predicting recurrence, progression, and survival rates. Low- and high-risk NMIBC can be considered two biologically different entities with different targeted treatment approaches. Carcinoma *in situ* (CIS) is a prime example. Despite being non-invasive, its aggressive nature and high risk of progression to muscle-invasive cancer imply that accurate and prompt histological diagnosis is essential to allow tailoring of management to achieve optimal patient outcomes.

Intravesical Bacillus Calmette-Guérin immunotherapy uses live attenuated *Mycobacterium tuberculosis* to induce cytotoxic effects on malignant urothelial cells. It is considered the current gold standard adjuvant therapy for superficial bladder tumors with a high risk of recurrence and progression. The European Association of Urology (EAU) guidelines suggest that intermediate-risk patients should receive 1 year of full-dose BCG therapy and that high-risk patients should receive up to 3 years of this treatment.[3] However, BCG therapy fails in about 40 % of patients with NMIBC.[4] This presents a significant clinical dilemma for the treatment of high-grade T1 bladder cancer and CIS, given their greater propensity for progression to muscle-invasive disease.

In this review, we discuss the mechanisms of action of BCG in the treatment of bladder cancer, the definition of BCG failure, and provide an overview of the treatment options available for patients with BCG-resistant high-risk NMIBC.

Bacillus Calmette-Guérin mechanisms of action

BCG is arguably one of the most successful immunotherapeutic agents for treating high-risk NMIBC. Numerous studies have investigated the specific mechanism underlying the efficacy of BCG in treating bladder cancer. Currently, no factors predicting BCG treatment failure have been identified. Both the EAU and American Urology Association (AUA) guidelines have added additional stratification criteria, with the addition of the fourth-highest risk NMIBC group. It is recommended that this group is offered upfront radical cystectomy, as they may have an increased risk of disease progression, despite BCG treatment. However, this remains a recommendation, and some surgeons still offer the gold-standard BCG treatment as a first-line treatment, particularly for older patients and those with comorbidities. A clear and thorough understanding of these pathways is crucial for combating BCG resistance and facilitating the improvement of these patients. We expound on some of the primary hypotheses below.

Side effects and tolerability of intravesical Bacillus Calmette-Guérin treatment

Although BCG is the main treatment modality for high-risk patients with NMIBC, not all patients are able to complete the treatment course due to local or systemic side effects.

Lamb et al. reported a dropout rate of >35 % in their initial BCG-treatment cohort. The most common side effects included dysuria and frequency, which were present in 95 % and 83 % of patients, respectively. Less common symptoms included hematuria, fever, and nausea.[5] Although less common, systemic side effects are often serious and potentially life-threatening. Sepsis due to severe pneumonitis or prostatitis requires specialist attention and long antibiotic courses. Most of these side effects are due to BCG entering the bloodstream through the bladder if administered too early after transurethral resection of a bladder tumor (TURBT) or via traumatic catheterization.[6,7] To minimize the risk of this occurrence, BCG administration should be deferred for at least 6–8 weeks post-TURBT. In addition, BCG therapy should be withheld in cases of traumatic catheterization or active infection. Other

long-term effects of BCG treatment include bladder fibrosis and contracture, although these occurrences are extremely rare and have only been documented in case reports.[8,9]

Mechanisms underlying cell apoptosis and necrosis

An *in vitro* study of human cells has shown that BCG increases the production of the intrinsic apoptotic pathway protein caspase-8 by upregulating toll-like receptor (TLR)-7. Yu et al. demonstrated that TLR activation plays a central role in the maturation of key immune modulators, including type-1 T helper cells, by the production of interleukin-12 and various other cytokines.[10] TLR overexpression in non-muscle-invasive urothelial cancer cells has been shown to inhibit urothelial cell proliferation, increase phagocytic activity, and result in a pro-apoptotic effect. Interestingly, lower-grade urothelial cancer cells appeared to express TLR-7 at higher concentrations than high-grade tumor cells. This phenomenon may contribute to the development of BCG-resistant diseases.

Sandes et al. studied the role of lysosomal hydrolase cathepsin B (CB) in the induction of apoptosis. They illustrated that BCG could activate pro-caspase-9 and the apoptotic BID protein by upregulating lysosomal CB to induce apoptosis in transitional cancer cell lines.[11] Furthermore, electron microscopy of tumor cells pretreated with apoptosis inhibitors has shown that BCG induces caspase-independent ultrastructural changes via the upregulation of high-molecular group box protein 1 (HMGB1).[12] These findings suggested that BCG induces a direct cytotoxic effect on bladder cancer cells via both apoptosis and necrosis.

Immune modulation

The attachment of BCG to urothelial cells is the initial step in an immune-mediated response. Fibronectin attachment protein, expressed on the cell wall surface of BCG, binds to fibronectin, a protein found in both healthy and malignant urothelial cells.[13] The ability of bladder cancer cells to internalize BCG is a key step in its antitumor activity. Multiple studies have suggested that phagocytosis plays a role in the internalization of BCG, with poorly differentiated cell lines being more susceptible than well-differentiated cell lines. *In vitro* studies conducted by Bevers et al. have demonstrated the ability of poorly differentiated cell lines, such as J82, to upregulate the cytokine interleukin (IL)-6, which plays a key role in the process of BCG internalization.[14] This upregulation increases the expression of fibronectin receptor subunits, thereby increasing BCG adherence to transitional cancer cells.[15]

Once internalized, the cellular response to BCG is primarily modulated by TLR. BCG stimulates a variety of TLR molecules, including TLR-1, -4, -7, and -9. Once activated, TLR molecules potentiate activation of the nuclear factor (NF)-kB pathway. NF-kB is an inducible transcription factor responsible for regulating gene transcription in a wide array of innate and adaptive immune pathways. It promotes cytokine transcription and naïve T cell differentiation into CD4$^+$ T helper and CD8$^+$ cytotoxic T cells.[16] Through these mechanisms, BCG exerts its immune effects and potentiates the cytotoxicity and phagocytosis of cancer cells.

Urine cytology after BCG instillation has revealed the presence of cytokines, such as IL-6 and -8. These cytokines are thought to recruit neutrophils. Besides their active role in phagocytosis, neutrophils release tumor necrosis factor-related apoptotic ligands (TRAILs). This discovery highlights the ability of BCG to stimulate a tumor-specific response.[3]

Finally, BCG stimulates macrophage production, which expresses nitric oxide. Unregulated NO production increases oxidative stress and deoxyribonucleic acid (DNA) damage and disrupts cellular energy metabolism and calcium homeostasis because of altered gene expression and p53 activation.[16] These changes are brought about by the activation of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP), adenosine triphosphate (ATP) depletion, and induction of the mitochondrial transition pore, which alters ion gradients and causes cellular swelling. The extent of cell injury is the key to determining whether a cell

undergoes necrosis or apoptosis. A significant disruption of mitochondrial ATP synthesis generally results in cell death via necrosis, while cells undergo apoptosis when mitochondrial ATP synthesis is maintained.[16]

BCG has a prominent immunotherapeutic profile, with activation of a multitude of key immune pathways, resulting in cell death via both apoptosis and necrosis.

Definition of Bacillus Calmette-Guérin failure

The term "BCG failure" has been inconsistently defined in the literature. This refers to the recurrence or progression of the disease after BCG therapy. The EAU guidelines consider BCG treatment to have failed in the following situations: (1) wherever muscle-invasive disease is detected during follow-up; (2) if a high-grade non-muscle-invasive tumor is present after either 3 or 6 months; or (3) if the disease shows any worsening, such as a higher number of recurrences, higher grade of disease, or appearance of CIS despite the initial presence of a response.[17] The EAU uses four individual terms: BCG-unresponsive, BCG-refractory, BCG-relapsing, and BCG-intolerant, to classify BCG failure further, as outlined in Table 1.[18] Interestingly, low-grade recurrence is not included in the BCG failure classification.

The timing, number of instillations, and grade of disease at recurrence influence the decision to continue BCG therapy or to abandon it and consider other treatment options. In a patient's treatment course, it is critical not to delay appropriate further intervention, that is, radical cystectomy. For example, the early recurrence of high-grade T1 disease with CIS after BCG therapy is associated with far worse outcomes than delayed recurrence of low-grade disease, prompting the need for earlier intervention. Previously published data have reported an increased risk of progression and metastasis in patients with two prior BCG failures as compared to those with only one failure.[19] Similarly, CIS recurrence within 12 months of BCG therapy confers a risk of worse outcomes than CIS recurrence after 12 months.

Guidelines for the appropriate management of BCG-refractory diseases also appear to differ. The EAU guidelines suggest a second course of BCG if high-grade T1 disease is present at the primary 3-month cystoscopy check-up. In contrast, the National Cancer Institute (NCI) recommends that such patients be referred for radical cystectomy.[17] Herr and Sogani demonstrated that the inability to attain a disease-free state by 6 months after BCG instillation corresponded to an increase in tumor recurrence and progression. They also found that early cystectomy, <2 years after the initial BCG treatment, offered a greater survival advantage than later treatment, with 92 % and 56 % survival rates at 96 months, respectively.[20]

Accurate comparison of study results regarding treatment outcomes is challenging due to the varied definition of BCG failure. Therefore, a data-driven, uniform definition of BCG-unresponsive disease is required to construct a timely escalation pathway for patients at increased risk of progression.

Bacillus Calmette-Guérin failure mechanism and predictive biomarkers

In the context of this limited treatment window and in the era of global BCG shortages, predicting or identifying patients who will not respond to BCG therapy has become increasingly important. Targeting BCG therapy in patients who are likely to gain an advantage can reduce their exposure to local and systemic side effects. The development of predictive biomarkers that can be measured prior to the start of treatment to evaluate the likelihood of a response to a specific therapy and to monitor the effectiveness of treatment is increasingly of interest. Biomarkers focus on detecting tumor microenvironment (TME) molecular changes that can be measured in tissues, serum, and, uniquely in bladder cancer, in urine. The TME is affected by genetic, immune, and metabolic changes.[21] Tissue biomarkers such as p53 and Ki67, which are potent cell cycle regulators, have been examined as possible predictors of BCG success.[22] Studies have suggested that p53 is not predictive; however, Ki67 has been demonstrated to predict recurrence following BCG therapy. These markers were examined in panels after BCG therapy to predict progression or recurrence; however, no correlation was observed.[22] Immune TME is another area of interest. Pichler et al. noted that a pre-treatment TME with high concentrations of $CD25^+$ regulatory T cells and tumor-associated macrophages (TAMs), and decreased Th2-predominant $CD4^+$ levels were predictive of worse recurrence-free survival (RFS) post-therapy.[23] Lim et al. demonstrated that the TME of BCG-responders was enriched with active $CD8^+PDL-1(-)$ and non-regulatory $CD4^+FOXP3(-)$ T cells; however, the TME of non-responders was enriched with exhausted $CD8^+PDL-1(+)$ T cells.[24]

Serum biomarkers, such as circulating tumor cells (CTC), circulating tumor DNA (ct-DNA), and serum ribonucleic acid (RNA) have been examined for use in bladder cancer. A systematic review demonstrated that six serum microRNAs (miRNAs: miR-21, miR-143, miR-155, miR-214, and miR-222) were predictive of early disease recurrence and progression in NMIBC.[25] Urine biomarkers have focused on the mechanisms of BCG response. In one pilot study, patients with higher levels of IL-8, measured 6-h post-BCG instillation, had a lower rate of progression and recurrence.[22] Interestingly, however, higher baseline levels of IL-8 in urine and peripheral blood leukocytes correlated with a higher risk of tumor recurrence, which highlights the complexity of baseline and stimulated cytokine expression and kinetics.[22] Cytokine panels have been developed to overcome these limitations. One such panel is the Cytokine Panel for Response to Intravesical Therapy (CyPRIT) nomogram, which uses nine inducible urinary cytokines and was developed at the MD Anderson Cancer Center to predict the likelihood of recurrence, with 85.5 % accuracy.[26] The second urinary biomarker is UroVysion, which uses a fluorescence *in situ* hybridization (FISH) assay to detect aneuploidy in chromosomes 3, 7, and 17 with the loss of chromosome 9p21. Studies conducted during BCG therapy and follow-up suggested that a positive FISH result at any time is suggestive of recurrence and progression.[22] Currently, no predictive biomarkers have been approved for bladder cancer by the Food and Drug Administration (FDA). This reflects the heterogeneity of NMIBC and the complexity of the mechanism of action of BCG, and the difficulty in the prediction of the elicited immune response.

Current treatment options

Although radical cystectomy remains the default treatment option for patients in whom BCG treatment fails, other bladder preservation options are becoming available, and many studies have concluded that these treatments are safe and effective.

Tables 2 and 3 summarize these studies, and provide more detail on the current treatment options recommended by the American and European guidelines.

Table 1
"BCG failure classification."[18]

BCG failure stratification	Definition
BCG-unresponsive	HG T1 at the first evaluation following induction BCG (3 months)
	Recurrent HG Ta/T1 within 6 months of adequate BCG treatment
	Recurrent CIS within 12 months of the last adequate BCG treatment
BCG-refractory	HG T1 at the first evaluation following induction BCG (3 months)
	Persistent/recurrent HG Ta/CIS following adequate BCG (6 months)
BCG-relapsing	HG recurrence after reaching a disease-free state within 6 months of receiving adequate BCG
BCG-intolerant	Disease recurrence/persistence after failure to receive adequate BCG therapy due to severe adverse effects

BCG: Bacillus Calmette-Guérin; CIS: Carcinoma *in situ*; HG: High-grade; Ta: Tumor invading the bladder mucosa; T1: Tumour invading the lamina propria.

Table 2
Studies in Bacillus Calmette-Guérin failure treatment options with published results.

Type of therapy	Progress	Results	Outcome
Intravesical			
Interferon + BCG[27]	Phase II	No benefit over BCG alone	Not in practice
Mitomycin combined with BCG for bladder cancer[28]	Phase I	Not published	Not in practice
Gemcitabine[29]	Phase II	Disease free: 3 months, 47 % 1 year, 28 % 2 years, 21 %	Used per clinician discretion
Docetaxel[30]	Single-institution study	Complete response after induction, 59 % 1-year RFS, 40 % 3-year RFS, 25 %	Used per clinician discretion
Combination of gemcitabine and docetaxel	Under investigation		
Device assisted			
Radiofrequency-induced thermo-chemotherapy (Synergo® system)[31]	Phase III	No significant difference in DFS between treatment arms	Recommended by EAU guidelines
Recirculation of heated chemotherapy called HIVEC[32]	Multi-center prospective study	Median DFS, 17.7 months 1-year cumulative incidence rate of disease recurrence/progression, 53 %	Used per clinician discretion
EMDA + MMC[33]	Phase II	3-year DFS TaG3, 75 % T1G3, 71.4 % CIS, 50 % TaT1G3 + CIS, 25 %	Used per clinician discretion
Intravesical immunotherapy			
NCT 02808143[28]	(Intravesical) pembrolizumab and BCG solution for treating patients with recurrent NMIBC	To determine the maximum tolerated dose of pembrolizumab when administered intravesically in combination with BCG in patients with high-risk or BCG-refractory NMIBC	Completed and results published
NCT 03759496[28]	Intravesical administration of durvalumab (MEDI4736) to patients with HR NMIBC. A phase II study with correlative	To assess the maximum tolerated dose of durvalumab given intravesically to patients with BCG-refractory NMIBC – Possibility of a rate of high-grade relapse-free after the initiation of durvalumab – Efficacy of intravesical administration of durvalumab in patients with BCG-refractory NMIBC	Completed and results published

BCG: Bacillus Calmette-Guérin; CIS: Carcinoma *in situ*; DFS: Disease-free survival; EAU: European Association of Urology; EMDA: Electromotive drug administration; HIVEC: Hyperthermic intravesical chemotherapy; MMC: Mitomycin C; NCT: National Clinical Trial; NMIBC: Non-muscle-invasive bladder cancer; RFS: Recurrence-free survival.

Microwave-induced hyperthermia with intravesical mitomycin C installation

Patients who develop recurrence during BCG treatment or those who cannot tolerate the side effects have limited alternative options. One emerging treatment involves the use of microwave-induced hyperthermic mitomycin C (MMC). It involves the administration of a combination of intravesical MMC and radiofrequency energy at 915 MHz to induce cell death. Medical Enterprise (Synergo) machines have been used for >15 years and have been reported to have good oncological outcomes. This technology utilizes an 18-French (Fr) urethral catheter that is inserted while the patient is in the clinic. Two cycles of chemotherapy (40 mg MMC) are administered through the catheter, for 30 min. The bladder wall is heated to a temperature of around 40.5–41.5 °C. The catheter is connected to a machine via thermocouples to control temperature changes. A study published in the *Journal of Urology* demonstrated a clear increase in the efficacy of chemotherapeutic MMC when combined with localized hyperthermia, as opposed to standard intravesical chemotherapy. One potential explanation is that tumor cells demonstrate a higher rate of MMC uptake under hyperthermic conditions or that the drug itself becomes more activated at higher temperatures.[34] A systematic review of published data showed a 59 % reduction in the recurrence of non-muscle-invasive disease with heated MMC compared to MMC alone.[35]

Overall, hyperthermic MMC has been shown to be a well-tolerated treatment with few side effects, providing scope as a salvage treatment in patients in whom BCG treatment has failed.

Intravenous immunotherapy

Recently, several promising developments have been achieved in systemic immune checkpoint inhibitors for BCG-unresponsive bladder cancer. Immune checkpoints are cell surface molecules that influence immune responses. In bladder cancer, programmed cell death protein 1 (PD-1) and its ligand (PDL-1), which downregulate the immune response to cells, have been of particular interest. PD-1 is expressed on T and B lymphocytes and macrophages, whereas PDL-1 is expressed on antigen-presenting cells. The binding of PD-1 to PDL-1 prevents T cell activation. Inhibitors of PD-1 and PDL-1 prevent binding and, therefore, allow T cell activation. Currently, the Food and Drug Administration (FDA) has approved several PD-1 and PDL-1 inhibitors for use in bladder cancer. These are primarily used as second-line therapies in advanced disease.[36] Only pembrolizumab has obtained FDA approval for use in BCG-unresponsive diseases with CIS.[37] The approval was based on the Keynote 057 phase II trial data,[38] which demonstrated a complete response in 46 % of patients, lasting at least 12 months. Investigation into other PD-1 and PDL-1 immune checkpoint inhibitors is ongoing, with

Table 3
Studies in Bacillus Calmette-Guérin treatment failure that are awaiting results, publication, or in recruitment phase.[28]

Trial No.	Study title	Primary aims	Status
NCT 02365818	Safety and efficacy of CG0070 oncolytic virus regimen for high-grade NMIBC after BCG failure	To study the safety and efficacy of CG0070, an oncolytic virus expressing GM-CSF, in patients with high-grade NMIBC in whom BCG therapy failed and who refused cystectomy.	Completed and results submitted but not published
NCT 02202772	Intravesical cabazitaxel, gemcitabine, and CGC in the treatment of urothelial carcinoma of the bladder	To assess the safety, toxicity, and efficacy of a novel multidrug intravesical regimen consisting of CGC in the treatment of BCG-resistant non-muscle-invasive urothelial carcinoma of the bladder.	Recruiting
NCT 04172675	A study of erdafitinib versus investigator choice of intravesical chemotherapy in participants who received BCG and recurred with high-risk NMIBC	To evaluate RFS in participants treated with erdafitinib *vs.* investigator's choice, for participants with high-risk NMIBC who harbor *FGFR* mutations or fusions, and who developed recurrence after BCG therapy.	Active, not recruiting
NCT 05644041	Intravesical gemcitabine in patients with NMIBC	To gain a better understanding of the use of gemcitabine intravesical chemotherapy for NMIBC in a prospective cohort of patients.	Recruiting
NCT 04752722	LEGEND study: EG-70 in NMIBC patients BCG-unresponsive and High-Risk NMIBC incompletely treated with BCG or BCG-naïve	To evaluate the safety and efficacy of intravesical administration of EG-70 and its effect on bladder tumors in patients with NMIBC. This study consists of two phases; a phase 1 dose-escalation to establish safety and recommend the phase 2 dose, followed by a phase 2 study to establish the effectivity of the treatment. The study will include patients with NMIBC who are unresponsive to BCG therapy and for whom radical cystectomy is recommended, or HR NMIBC patients who are BCG-naïve or have received incomplete BCG treatment.	Recruiting
NCT 02844816	Atezolizumab in treating patients with recurrent BCG-unresponsive NMIBC	To estimate complete response at 25 weeks after registration for those with a CIS component and to evaluate event-free survival at 18 months in patients with BCG-unresponsive HR NMIBC treated with atezolizumab.	Active, not recruiting

BCG: Bacillus Calmette-Guérin; CGC: Cabazitaxel, gemcitabine, and cisplatin; CIS: Carcinoma *in situ*; GM-CSF: Granulocyte-macrophage colony-stimulating factor; FGFR: Fibroblast growth factor receptor; NCT: National Clinical Trial; NMIBC: Non-muscle-invasive bladder cancer; RFS: Recurrence-free survival.

several phase II and III trials due to report results in the next few years. The SWOG S1605 phase II trial with atezolizumab showed promising preliminary results, with a 41.1 % complete response at 3 months. The PREVERT phase II trial is currently investigating avelumab in combination with radiotherapy (RT). Durvalumab in combination with RT or BCG is currently being analyzed in an ADAPT-BLADDER phase II study. Nivolumab monotherapy and its use in combination with BCG is being investigated in the CheckMate 9UT trial,[39] while pembrolizumab in combination with BCG therapy is under investigation in the Keynote-676 trial.[40]

A second promising immunotherapy is gene therapy, with the novel intravesical agent nadofaragene firadenovec, which was approved by the FDA in January 2023[41] and was discussed in the EAU guidelines 2023.[18] With nadofaragene firadenovec, the human interferon alpha 2b (*IFNα-2b*) gene is transfected into cancer cells via the non-replicating adenovirus. The gene is incorporated into cellular DNA, resulting in the synthesis and expression of the human IFNα-2b protein, increasing IFNα levels in urine, which has an apoptotic effect on cancer cells. In a single-arm, open-label, repeat-dose clinical trial, a complete response was observed at 3 months in 53.4 % of patients following the administration of one dose.[42]

Radical cystectomy

Radical cystectomy remains the treatment of choice for BCG-resistant bladder cancer, particularly in patients with CIS, as per the EAU guidelines. Similarly, Canadian guidelines outline that patients with high-risk NMIBC should be presented with the option of cystectomy in the first instance. The advantage of this treatment is clear, with several studies highlighting improved disease-free survival in patients referred directly for cystectomy after initial recurrence. However, cystectomy is a major procedure linked to significant morbidity, and therefore may not be an option for patients with co-existing health conditions. Further research into viable, less-invasive treatment options is required. Cystectomy is not suitable for frail and older patients or for those who are keen to preserve their bladders. With advances in robotic surgery, the morbidity associated with cystectomy has decreased. However, it carries a 3 % risk of death within 30 days.[43]

Over the long term, the EAU guidelines quote morbidity with urinary diversion in 45 % of patients at 5 years,[44] which increases to 94 % at 15 years.[44] Complications include vitamin B12 deficiency, metabolic acidosis, worsening of renal function, upper urinary tract (UUT) infections, UUT morphological changes, urolithiasis, and ureteroenteric anastomosis.[45] Complications can affect patients' quality of life postoperatively, requiring further health care services, including further surgery.

This study had several limitations. A uniform definition of BCG-resistant bladder cancer is lacking. Research on this topic is limited. In turn, BCG outcomes may vary depending on individual definitions of "BCG failure."

Conclusions and future directions

BCG therapy continues to play a significant role in the treatment of NMIBC. Patients with BCG-non-responsive NMIBC represent a heterogeneous group with differing outcomes based on the speed and nature of disease recurrence. Various urological bodies use different criteria to define such disease, with varied guidelines for ongoing management.

However, the literature has consistently proven that muscle-invasive diseases have significantly worse outcomes when treatment is delayed. Nevertheless, as radical cystectomy has significant morbidity, further

research is required to improve patient selection into less invasive treatment options. Bladder preservation therapies either in the form of intravesical therapy or systemic treatment remain under investigation with variable oncological advantages.

Furthermore, studies that look into the clinical and histological parameters that could be used to identify patients at high risk of recurrence and progression to muscle-invasive disease are ongoing. Further research into new treatment methods and the identification of predictive biomarkers are required to improve survival outcomes in patients with BCG-resistant bladder cancer. Further advances and molecular subtyping have facilitated the selection of patients with muscle-invasive bladder cancer to receive neoadjuvant chemotherapy, with the hope that a similar pattern could be followed in NMIBC. In addition, the advancement of gene therapy might present a breakthrough in the treatment of this challenging condition. However, these studies are in their inception, and further research is required.

Authors contribution

Paper concept and design: Hanna Maroof, Ahmed Ali. The first draft of the manuscript was written by Hanna Maroof, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics statement

None.

Data availability statement

The supporting data for this paper have been published, are referenced, and are available online.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. WCRF International. Bladder cancer statistics. London: World Cancer Research Fund International, (n.d.). Available from: https://www.wcrf.org/cancer-trends/bladder-cancer-statistics/. [Last accessed on 21/August/2023].
2. Kaufman DS, Wu Shipley, Feldman AS. Bladder cancer. *Lancet.* 2009;374:239–249. https://doi.org/10.1016/S0140-6736(09)60491-8.
3. Han J, Gu X, Li Y, Wu Q. Mechanisms of BCG in the treatment of bladder cancer-current understanding and the prospect. *Biomed Pharmacother.* 2020;129:110393. https://doi.org/10.1016/j.biopha.2020.110393.
4. Zlotta AR, Fleshner NE, Jewett MA. The management of BCG failure in non-muscle-invasive bladder cancer: an update. *Can Urol Assoc J.* 2013;3(6 Suppl 4):S199–S205. https://doi.org/10.5489/cuaj.1196.
5. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance Bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group study. *J Urol.* 2000;163:1124–1129. https://doi.org/10.1016/S0022-5347(05)67707-5.
6. Lamm DL. Complications of Bacillus calmette-Guérin immunotherapy. *Urol Clin.* 1992;19:565–572. https://doi.org/10.1016/s0094-0143(21)00423-7.
7. Lukacs B, Cornu JN, Aout M, et al. Management of lower urinary tract symptoms related to benign prostatic hyperplasia in real-life practice in France: a comprehensive population study. *Eur Urol.* 2013;64:493–501. https://doi.org/10.1016/j.eururo.2013.02.026.
8. Yang C, Lv Z, Li Y. Reduction of bladder volume after BCG immunotherapy. *Urol Int.* 2021;105:155–158. https://doi.org/10.1159/000510167.
9. Barton Grossman H. Bladder contracture following intravesical bcg immunotherapy. *Urology.* 1993;41:353–355. https://doi.org/10.1016/0090-4295(93)90595-2.
10. Yu DS, Wu CL, Ping SY, Keng C, Shen KH. Bacille calmette-guerin can induce cellular apoptosis of urothelial cancer directly through toll-like receptor 7 activation. *Kaohsiung J Med Sci.* 2015;31:391–397. https://doi.org/10.1016/j.kjms.2015.05.005.
11. Sandes E, Lodillinsky C, Cwirenbaum R, Argüelles C, Casabé A, Eiján AM. Cathepsin B is involved in the apoptosis intrinsic pathway induced by Bacillus Calmette-Guérin in transitional cancer cell lines. *Int J Mol Med.* 2007;20:823–828. https://doi.org/10.3892/ijmm.20.6.823.
12. See WA, Zhang G, Chen F, Cao Y, Langenstroer P, Sandlow J. Bacille-Calmette Guèrin induces caspase-independent cell death in urothelial carcinoma cells together with release of the necrosis-associated chemokine high molecular group box protein 1. *BJU Int.* 2009;103:1714–1720. https://doi.org/10.1111/j.1464-410X.2008.08274.x.
13. Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nat Rev Urol.* 2014;11:153–162. https://doi.org/10.1038/nrurol.2014.15.
14. Bevers RFM, de Boer EC, Kurth KH, Schamhart DHJ. BCG-induced interleukin-6 upregulation and BCG internalization in well and poorly differentiated human bladder cancer cell lines. *Eur Cytokine Netw.* 1998;9:181–186.
15. Zhang GJ, Crist SA, Mckerrow AK, Xu Y, Ladehoff DC, See WA. Autocrine IL-6 production by human transitional carcinoma cells upregulates expression of the α5β1 fibronectin receptor. *J Urol.* 2000;163:1553–1559. https://doi.org/10.1016/s0022-5347(05)67678-1.
16. Murphy MP. Nitric oxide and cell death. *Biochim Biophys Acta.* 1999;1411:401–414. https://doi.org/10.1016/S0005-2728(99)00029-8.
17. Kamel MH, Bailey SL, Moore JT, Heshmat SM, Bissada NK. Definition of BCG failure in non-muscle invasive bladder cancer in major urological guidelines. *UroToday Int J.* 2011;4:art 82. https://doi.org/10.3834/uij.1944-5784.2011.12.15.
18. *Non-muscle-invasive bladder cancer. Disease management. Arnhem: European association of Urology (Uroweb)*; 2023. Available from: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/chapter/disease-management. [Accessed June 4, 2023].
19. Catalona WJ, Hudson MA, Gillen DP, Andriole GL, Ratliff TL. Risks and benefits of repeated courses of intravesical Bacillus Calmette-Guerin therapy for superficial bladder cancer. *J Urol.* 1987;137:220–224. https://doi.org/10.1016/s0022-5347(17)43959-0.
20. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol.* 2001;166:1296–1299. https://doi.org/10.1016/S0022-5347(05)65756-4.
21. Semeniuk-Wojtaś A, Poddębniak-Strama K, Modzelewska M, et al. Tumour microenvironment as a predictive factor for immunotherapy in non-muscle-invasive bladder cancer. *Cancer Immunol Immunother.* 2023;72:1971–1989. https://doi.org/10.1007/s00262-023-03376-9.
22. Hensley PJ, Lobo N, Bree KK, et al. Predictive biomarkers in the management of bladder cancer: perspectives in an evolving therapeutic landscape. *Soc Int Urol J.* 2022;3:245–257. https://doi.org/10.48083/RVZV1144.
23. Pichler R, Fritz J, Zavadil C, Schäfer G, Culig Z, Brunner A. Tumor-infiltrating immune cell subpopulations influence the oncologic outcome after intravesical Bacillus Calmette-Guérin therapy in bladder cancer. *Oncotarget.* 2016;7: 39916–39930. https://doi.org/10.18632/oncotarget.9537.
24. Lim CJ, Nguyen PHD, Wasser M, et al. Immunological hallmarks for clinical response to BCG in bladder cancer. *Front Immunol.* 2020;11:615091. https://doi.org/10.3389/fimmu.2020.615091.
25. Xie Y, Ma X, Chen L, et al. MicroRNAs with prognostic significance in bladder cancer: a systematic review and meta-analysis. *Sci Rep.* 2017;7:5619. https://doi.org/10.1038/s41598-017-05801-3.
26. Kamat AM, Briggman J, Urbauer DL, et al. Cytokine panel for response to intravesical therapy (CyPRIT): nomogram of changes in urinary cytokine levels predicts patient response to Bacillus Calmette-Guérin. *Eur Urol.* 2016;69:197–200. https://doi.org/10.1016/j.eururo.2015.06.023.
27. Gallagher BL, Joudi FN, Maymí JL, O'Donnell MA. Impact of previous bacille calmette–guerin failure pattern on subsequent response to Bacille Calmette–Guerin plus interferon intravesical therapy. *Urology.* 2008;71:297–301. https://doi.org/10.1016/j.urology.2007.09.050.
28. ClinicalTrials.gov. ClinicalTrials.gov is a place to learn about clinical studies from around the world. Bethesda: National Institutes of Health. Available from: https://clinicaltrials.gov/ct2/home. [Last accessed on 2023 October 25].
29. Skinner EC, Goldman B, Sakr WA, et al. SWOG S0353: phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical Bacillus Calmette–Guérin. *J Urol.* 2013;190: 1200–1204. https://doi.org/10.1016/j.juro.2013.04.031.
30. Barlow LJ, McKiernan JM, Benson MC. Long-term survival outcomes with intravesical docetaxel for recurrent nonmuscle invasive bladder cancer after previous Bacillus Calmette–Guérin Therapy. *J Urol.* 2013;189:834–839. https://doi.org/10.1016/j.juro.2012.10.068.
31. Tan WS, Panchal A, Buckley L, et al. Radiofrequency-induced thermo-chemotherapy effect versus a second course of Bacillus Calmette–Guérin or Institutional Standard in patients with recurrence of non-muscle-invasive bladder cancer following induction or maintenance Bacillus Calmette–Guérin therapy (HYMN): a phase III, open-label, randomised controlled trial. *Eur Urol.* 2019;75:63–71. https://doi.org/10.1016/j.eururo.2018.09.005.
32. de Jong JJ, Hendricksen K, Rosier M, Mostafid H, Boormans JL. Hyperthermic intravesical chemotherapy for BCG unresponsive non-muscle invasive bladder cancer patients. *Bladder Cancer.* 2018;4:395–401. https://doi.org/10.3233/BLC-180191.
33. Racioppi M, Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi PF. ElectroMotive Drug Administration (EMDA) of mitomycin C as first-line salvage

therapy in high risk "BCG failure" non muscle invasive bladder cancer: 3 years follow-up outcomes. *BMC Cancer*. 2018;18:1224. https://doi.org/10.1186/s12885-018-5134-7.

34. Van Der Heijden AG, Jansen CFJ, Verhaegh GW, O'donnell MA, Schalken JA, Witjes JA. The effect of hyperthermia on mitomycin-C induced cytotoxicity in four human bladder cancer cell lines. *Eur Urol*. 2004;46:670–674. https://doi.org/10.1016/j.eururo.2004.06.009.

35. Lammers RJM, Witjes JA, Inman BA, et al. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. *Eur Urol*. 2011;60:81–93. https://doi.org/10.1016/j.eururo.2011.04.023.

36. Wołącewicz M, Hrynkiewicz R, Grywalska E, et al. Immunotherapy in bladder cancer: current methods and future perspectives. *Cancers*. 2020;12:1181. https://doi.org/10.3390/cancers12051181.

37. *FDA approves pembrolizumab for BCG-unresponsive, high-risk non-muscle invasive bladder cancer*. Silver Spring: FDA; 2020. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer. [Accessed October 25, 2023].

38. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol*. 2021;22:919–930. https://doi.org/10.1016/S1470-2045(21)00147-9.

39. Albisinni S, Martinez Chanza N, Aoun F, et al. Immune checkpoint inhibitors for BCG-resistant NMIBC: the dawn of a new era. *Minerva Urol Nephrol*. 2021;73:292–298. https://doi.org/10.23736/S2724-6051.21.04309-5.

40. Kamat AM, Shore N, Hahn N, et al. KEYNOTE-676: phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC. *Future Oncol*. 2020;16:507–516. https://doi.org/10.2217/fon-2019-0817.

41. *FDA approves first gene therapy for the treatment of high-risk, non-muscle-invasive bladder cancer*. Silver Spring: FDA; 2022. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-high-risk-non-muscle-invasive-bladder-cancer. [Accessed October 25, 2023].

42. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol*. 2021;22:107–117. https://doi.org/10.1016/S1470-2045(20)30540-4.

43. Packiam VT, Pariser JJ. Association between perioperative morbidity and mortality after radical cystectomy: an opportunity to understand the complication snowball effect. *Transl Androl Urol*. 2019;8(Suppl 3):S261–S262. https://doi.org/10.21037/tau.2019.03.16.

44. Madersbacher S, Schmidt J, Eberle JM, et al. Long-term outcome of ileal conduit diversion. *J Urol*. 2003;169:985–990. https://doi.org/10.1097/01.ju.0000051462.45388.14.

45. Witjes JA, Bruins HM, Carrión A, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2023 guidelines. *Eur Urol*. 2023;79:82–104. https://doi.org/10.1016/j.eururo.2020.03.055.