

Novel and emerging approaches in the management of non-muscle invasive urothelial carcinoma

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Ther Adv Med Oncol

2021, Vol. 13: 1–14

DOI: 10.1177/
17588359211039052

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Abstract: Non-muscle invasive bladder cancer (NMIBC) has traditionally been managed with transurethral resection followed by intravesical chemotherapy and/or bacillus Calmette–Guerin (BCG) in a risk-adapted manner. These tumors commonly recur and can progress potentially to lethal muscle invasive disease. A major unmet need in the field of NMIBC is bladder preserving therapy for recurrent high-grade NMIBC after adequate intravesical BCG therapy. The current gold standard treatment for these BCG-unresponsive patients is radical cystectomy, which is associated with considerable morbidity and mortality, particularly in older and frailer patients. It is therefore critical to provide alternative treatment options with acceptable oncological outcomes. In this review we explore novel bladder-sparing treatment options including combination intravesical therapy, enhanced instillation methods, immunotherapy, gene therapy, targeted therapy, photodynamic therapy and BCG variants across the spectrum of NMIBC disease states, ranging from low grade BCG-naïve patients through to high-grade BCG-unresponsive NMIBC.

Keywords: BCG-unresponsive bladder cancer, immunotherapy, intravesical BCG, intravesical chemotherapy, non-muscle invasive bladder cancer, novel therapies

Received: 29 April 2021; revised manuscript accepted: 26 July 2021.

Introduction

Approximately 75% of urothelial bladder cancers are non-muscle invasive bladder cancer (NMIBC), making it critically important to develop novel means to optimize management in this patient subgroup.¹ These tumors are typically managed by transurethral resection followed by adjuvant intravesical instillations to reduce the risk of recurrence and progression. Current treatment of NMIBC is based on stratification into low, intermediate and high-risk groups.² Low-risk tumors are conventionally managed with single dose intravesical chemotherapy while high-risk tumors are managed with adjuvant intravesical bacillus Calmette–Guerin (BCG). Intermediate-risk tumors may be managed with either intravesical chemotherapy or BCG dependent on patient, disease and clinician factors.

BCG is the most effective intravesical agent in high-risk NMIBC.³ It acts primarily through

immune-mediated cytotoxicity involving both the innate [e.g. natural killer (NK) cells and granulocytes] and the adaptive (e.g. CD4+ and CD8+ lymphocytes) effector cells. BCG itself is also believed to have a direct effect on tumor cells.⁴

Standard intravesical BCG is successful in 60–70% of patients with NMIBC.⁵ High-grade recurrence after BCG presents a clinical challenge, and the optimal treatment of these patients remains unclear. The guidelines recommend radical cystectomy in these patients, with disease-free rates exceeding 90%.⁶ Bladder-sparing alternatives are limited. Novel therapeutic options for patients who recur after BCG are critical in order to reduce the number of patients needing cystectomy with its associated morbidity, while maintaining acceptable oncological outcomes. Many patients are unfit for cystectomy, and others decline cystectomy. The need for novel therapies is accentuated by BCG shortages which may

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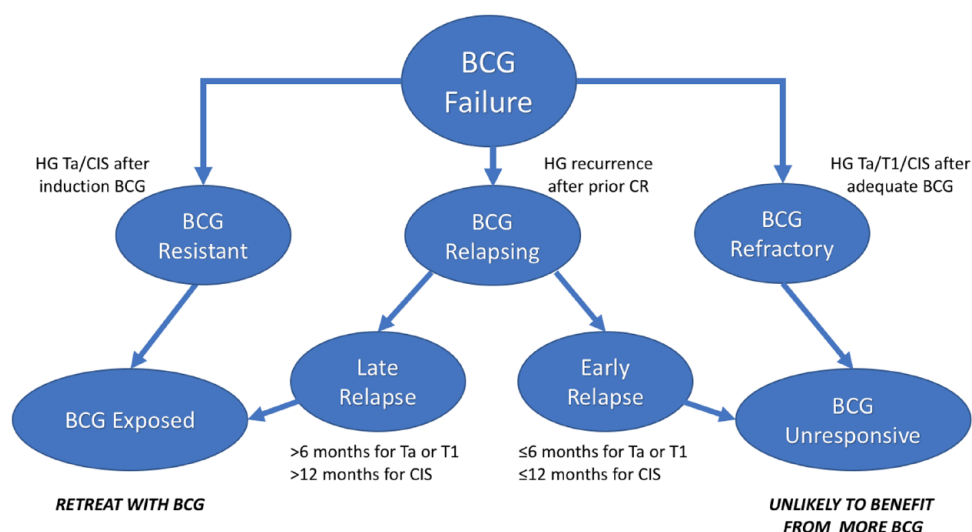


Figure 1. Disease states in high risk non-muscle invasive bladder cancer based on prior BCG therapy

impact supply in the future. In this review we will explore novel therapies for patients with NMIBC.

Methods

We performed a literature review using the search terms ‘novel’, ‘non muscle invasive bladder cancer’, ‘BCG unresponsive’ in Pubmed and Google Scholar. We used only English language papers published after 1990. A similar search with the above terms was undertaken on clinicaltrials.gov to identify ongoing trials with novel treatments. We focused on phase II/III trials. References from selected articles were also checked to ensure completeness.

In this narrative review we will explore novel therapies according to the disease state in which they are primarily being developed: BCG-naïve, BCG-exposed and BCG-unresponsive. Due to historical inconsistencies in definitions of BCG failure and adequate BCG therapy, most studies do not distinguish ‘BCG unresponsive’ from ‘BCG exposed’.

NMIBC disease states

NMIBC disease states are defined by tumor grade and stage as well as prior BCG therapy (Figure 1 and Table 1). Intermediate and high-risk tumors are considered separately. Patients who have never received intravesical BCG are considered ‘BCG-naïve’. The term ‘BCG-unresponsive’ has evolved to encompass high-risk patients in whom additional intravesical BCG therapy is unlikely to be effective.⁷

Between these two groups are the patients with ‘BCG-exposed’ or ‘BCG-experienced’ NMIBC, who have received some BCG, but do not meet specific criteria for BCG-unresponsive NMIBC.

BCG-unresponsive comprises both BCG-refractory and early BCG-relapsing patients.⁸ In both instances, patients must have received adequate BCG therapy, which is defined as induction plus one round of maintenance or a second round of induction for patients with recurrent Ta or carcinoma *in situ* (CIS) disease, or simply one round of induction for patients with recurrent T1 tumors. In BCG-refractory patients adequate BCG fails to clear the disease, whereas in BCG-relapsing patients, high-risk NMIBC recurs after initial response. 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.⁹

BCG-exposed patients typically recur after BCG induction therapy alone, meaning that they have not received ‘adequate’ BCG to be considered unresponsive, or they have a late relapse. The timing of relapse has important prognostic implications; an early relapse has a similar outcome to BCG-refractory disease, but late relapses may respond to additional BCG¹⁰ and generally have a more favorable outcome.^{9,11} Similarly, patients with Ta or CIS disease after induction BCG alone can be treated with additional BCG.

The natural history of BCG-refractory disease that is not managed with timely cystectomy is

Table 1. Definitions of high-risk non-muscle-invasive bladder cancer disease states.

Disease state	Definition
BCG-naïve	No prior exposure to intravesical BCG therapy
BCG-resistant	High-grade Ta or CIS that is persistent/recurrent at the time of first assessment after induction BCG (typically 3 months after pre-treatment TURBT)
BCG-refractory	<ol style="list-style-type: none"> 1. High-grade Ta or CIS that is persistent/recurrent at the time of first assessment after induction and one round of maintenance (or second induction) BCG (typically 6 months after pre-treatment TURBT) 2. T1 tumor that is persistent/recurrent at the time of first assessment after induction BCG (typically 3 months after pre-treatment TURBT)
BCG-relapsing	Recurrent high-grade Ta/T1/CIS after prior complete response to BCG
Early	- Ta/T1 within 6 months and CIS within 12 months of last dose of BCG
Late	- High-grade recurrence later than stated time windows for early relapse
BCG-unresponsive	Composite disease state including BCG refractory and early relapse in patients who received at least five doses of induction BCG and two doses of maintenance (or second induction) BCG
BCG-exposed	High-grade recurrence after induction BCG only (includes BCG resistant) or late relapse
BCG-intolerant	Patient discontinued BCG due to adverse effects

BCG, bacillus Calmette–Guerin; CIS, carcinoma *in situ*; TURBT, transurethral resection of bladder tumor.

often progression to muscle-invasive cancer, metastasis, and even death.¹² Historical data suggest that the risk of metastasis in patients with BCG failure reaches 50% after three additional cycles of BCG.¹³ The need for novel bladder preserving therapies is therefore particularly acute for these patients.

A thorough review of established treatment options for BCG-unresponsive patients is beyond the scope of this review. Bladder preserving options include intravesical valrubicin, which was found to have a recurrence-free survival rate of only 8% at 30 months, and BCG with interferon-alpha, which has now been withdrawn from the market.^{14,15} Single agent intravesical chemotherapy with gemcitabine, mitomycin or docetaxel remains an option, but with low rates of durable response.^{16,17} Trimodal therapy can also be considered for BCG-unresponsive T1 disease although studies have been limited primarily to BCG-naïve disease.¹⁸ None of these therapies have been adequately studied in well-designed trials using current disease state definitions. As a result, there is no clearly defined standard bladder preserving treatment option for patients with BCG-unresponsive high-risk NMIBC.

Novel therapies for BCG-unresponsive high-risk NMIBC

Only the most recent clinical trials have clearly distinguished the BCG-unresponsive disease state, because this definition has only evolved in the past several years. Many prior trials enrolled heterogeneous patient populations that sometimes included both high-risk and intermediate-risk disease, and used various criteria for defining BCG failure. These will nonetheless be described here in the context of BCG-unresponsive high-risk NMIBC. This has become the focus of drug development for many stakeholders, as it is an area of great unmet need, and the path to US Food and Drug Administration (FDA) registration is clearest.¹⁹ The most recent trials have been single-armed trials in patients with BCG-unresponsive CIS. A summary of active phase II/III trials that have not yet reported results is provided in Table 2.

Combination intravesical chemotherapy

Recent efforts have focused on examining combination intravesical regimens for recurrences after prior BCG, including gemcitabine/docetaxel and cabazitaxel/cisplatin/gemcitabine.²⁰ A study of 45

Table 2. Ongoing trials in BCG failure NMIBC (phase II or later).

Enhanced intravesical chemotherapies						
Agent	Study	Study design	Inclusion criteria	Mechanism	Primary outcomes	
Photodynamic therapy	NCT03945162	Phase II single-arm	BCG-unresponsive CIS	Instillation of photosensitizer (TLD1433) followed by transurethral irradiation	CR rate	
Immunotherapy						
Agent	Study	Study design	Inclusion criteria	Mechanism	Primary outcomes	
Durvalumab	NCT03317158	Multi-arm phase II study comparing durvalumab +/-BCG +/-EBRT	BCG-exposed	PD-1 inhibitor	Phase I: Determine recommended combination doses Phase II: 6-month relapse-free survival (RFS)	
Pembrolizumab	NCT02625961 (KEYNOTE-057)	Phase II single-arm open-label	BCG-unresponsive CIS	PD-1 inhibitor	CR rate Disease-free survival rate	
Nivolumab +/-BMS-986205	NCT03519256	Phase II randomized open-label	BCG-unresponsive CIS	PD-1 inhibitor	CR rate	
Recombinant intravesical therapies						
Agent	Study	Study design	Inclusion criteria	Mechanism	Primary outcomes	
CG0070	NCT04452591	Phase III single-arm open-label	BCG-unresponsive CIS or papillary	GM-CSF-expressing oncolytic virus	CR rate	
Other therapies						
Agent	Study	Study design	Inclusion criteria	Mechanism	Primary outcomes	
TAR-200 +/- cetrelimab	NCT04640623	Phase II open-label TAR-200 versus cetrelimab versus cetrelimab + TAR-200	BCG-unresponsive CIS or papillary	PD-1 inhibitor (cetrelimab) + extended release intravesical gemcitabine (TAR-200)	CR rate	
CG0070 + pembrolizumab	NCT04387461	Phase II single-arm	BCG-unresponsive CIS	GM-CSF-expressing oncolytic virus + PD-1 inhibitor	CR rate	
Pembrolizumab + gemcitabine	NCT04164082	Phase II single-arm	BCG-unresponsive CIS or papillary	PD-1 inhibitor + chemotherapy	CR rate	
EG-70	NCT04752722	Phase I/II single-arm	BCG-unresponsive CIS	Non-viral gene therapy	CR rate	
Erdafitinib	NCT04172675	Phase II multi-arm randomized trial	BCG-unresponsive CIS or papillary tumor with FGFR alteration	Fibroblast growth factor receptor inhibitor	Recurrence-free survival	
BCG, bacillus Calmette-Guérin; CIS, carcinoma <i>in situ</i> ; CR, complete response; FGFR, fibroblast growth factor receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; NMIBC, non-muscle invasive bladder cancer.						

patients with high-risk NMIBC (90% with prior BCG) treated with gemcitabine/docetaxel revealed 34% to be free of disease at 2 years.²¹ Response rates were higher in BCG-relapsing compared with BCG-refractory patients and 30% underwent cystectomy before the end of the study period. A more recent multi-institutional study retrospectively reviewed 276 patients with recurrent NMIBC after prior BCG, including BCG-intolerant, BCG-exposed and BCG-unresponsive ($n=105$) patients. One and 2-year high-grade recurrence-free survival was 65% and 52%, respectively.²² This combination has become popular in North America.

Device-assisted intravesical chemotherapy

The efficacy of intravesical chemotherapy is limited by short dwell time in the bladder and inadequate penetration into bladder tumor tissue. Novel approaches use either electrical current or heat to enhance drug uptake into the urothelium. Electromotive mitomycin C (EMDA-MMC) uses a catheter electrode to run current through the bladder wall and improve the penetration of mitomycin. EMDA-MMC has been examined as a possible alternative for intermediate-risk disease and in combination with BCG for high-risk disease;²³ however, few studies to date have reviewed it in the BCG-refractory space. A small prospective study of 26 BCG-refractory patients reported a 12-month high-grade disease-free survival of 72% for patients with papillary tumors, and 38% for those with CIS.¹³

Intravesical chemohyperthermia (CHT) can utilize external heating of the chemotherapeutic agent (combat bladder recirculation) or application of microwave energy to the bladder through a specialized catheter (Synergo) that heats the bladder wall to 41–44°C.²⁴ The latter device was used in a prospective study of patients with high and intermediate-risk NMIBC, 81% of whom had received prior BCG, to treat with MMC or epirubicin. The 2-year recurrence-free survival was 47%.²⁵ The HYMN randomized controlled trial (RCT) randomly assigned non-cystectomy candidates with high-grade recurrence after prior BCG to either intravesical CHT or institution standard salvage therapy.²⁶ The authors reported no difference in the primary outcome of complete response (CR) rate in CIS patients at 3 months, although the disease-free survival was actually worse with CHT than in the control arm in this subgroup of patients [hazard ratio (HR) 2.06,

95% confidence interval (CI) 1.17–3.62, $p=0.01$]. There was a trend towards improved disease-free survival in patients with papillary tumors treated with CHT (HR 0.5, HR 0.50, 95% CI 0.22–1.17, $p=0.11$), but the difference did not meet statistical significance. The HYMN study is noteworthy for being one of the few RCTs in patients with recurrent tumors after prior BCG, but it has been criticized for the heterogeneity in the control group and inadequate statistical power to perform subgroup analyses.

Intravesical taxanes have been successfully incorporated into micelles and investigated as potential salvage agents for BCG-refractory NMIBC. These nanoparticles are believed to act as mucoadhesives, improving the attachment of cytotoxic agents to the urothelium, increasing dwell time, and enhancing drug uptake.²⁷ A single-arm, phase II trial testing albumin-bound paclitaxel in 28 high-risk NMIBC patients with recurrence after BCG induction demonstrated recurrence-free survival of 18% and cancer-specific survival of 91% at a median follow-up of 41 months.²⁸

TAR-200 is a novel intra-vesical drug delivery system composed of gemcitabine and osmotic minitablets with urea as an active osmotic agent. The drug is given by an inserter every 3 weeks for 6 months and 3-monthly thereafter. This provides a slow release of the gemcitabine during the 3 weeks that the tablets are in the bladder, increasing dwell time and exposure. A phase II trial is currently underway comparing TAR-200 and cetrelimab (PD-1 inhibitor) each alone and in combination in BCG-unresponsive patients (NCT04640623).

Immunotherapy

Inhibitors of programmed cell death protein (PD1) and PD1 ligand (PDL1), (collectively termed immune checkpoint inhibitors) were approved for the treatment of metastatic bladder cancer post-platinum and in cisplatin-ineligible patients by the FDA in 2017.^{29,30} These agents represent a major breakthrough in the treatment of patients with metastatic bladder cancer. These agents interrupt negative regulatory signals that suppress tumor cell killing by activated T cells, thereby stimulating anti-tumor immune responses.

Pembrolizumab was approved by the FDA in January 2020 for the treatment of BCG-unresponsive CIS in patients ineligible for radical

cystectomy. The KEYNOTE-057 trial reported a 3-month CR rate of 40.2% in 96 patients with BCG-unresponsive CIS treated with intravenous pembrolizumab every 3 weeks for up to 2 years.³¹ The median duration of response was 16 months, so that 19% of patients were free of high-grade recurrence at one year. Radical cystectomy was required in 37.5% of patients but up-staging to muscle-invasive bladder cancer was observed in less than 10% of patients.³² Pembrolizumab is the first agent approved by the FDA for BCG-unresponsive NMIBC since valrubicin. It marks a key milestone in the development of novel therapeutics for this disease.

SWOG S1605 is a similar single-arm phase II study investigating systemic atezolizumab in the same disease state. Results from this trial indicate a CR rate of 41.1% at 3 months, 27.0% at 6 months and 14% at 18 months in patients with CIS.³³ Patients in this study underwent mandatory re-biopsy at 6 months, which was not required in KEYNOTE-057. In S1605 and KEYNOTE-057 the rate of grade 3–5 adverse events was 13–16%, including one treatment-related death in S1605.³³

Preliminary data on intravesical administration of the interleukin (IL)-15R α Fc superagonist N-803 were presented at the 2021 Genitourinary Cancer Symposium in February 2021. This agent is a chimeric protein consisting of a mutated IL-15 fused to the alpha-subunit of the IL-15 receptor and the crystallizable fragment (Fc) domain of an antibody. IL-15 serves as a positive regulator of NK and T-cell activation. The N-803 combination affords increased stability and stimulation of the IL-15 receptor. The QUILT study treated BCG-unresponsive CIS patients with combination intravesical BCG and N-803 according to the traditional SWOG protocol for induction and maintenance BCG. Re-induction was allowed after 3 months for persistent disease. The authors reported a 71% CR rate (at 3 or 6 months) that lasted a median 19.2 months. Furthermore, 88% of patients in the trial remained cystectomy free.

Atezolizumab and pembrolizumab have been tested in BCG-unresponsive papillary (Ta/T1) NMIBC. Those results have been reported only for atezolizumab, for which the event-free survival was 65% at 6 months and 47% at 18 months in the S1605 trial.³³ The combination of intravesical chemotherapy (gemcitabine) with immune checkpoint inhibition (pembrolizumab) is being tested in the Alliance A031803 trial (NCT04164082)

and the combination of immunotherapy with other novel agents represents a promising path towards better outcomes in BCG-unresponsive patients. Immunotherapy represents a potential paradigm change for the management of patients with NMIBC that would require close collaboration between urologists and medical oncologists.

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. Nadofaragene firadenovec is a replication-deficient adenovirus programmed to express interferon-alpha (IFN- α). It is administered together with an incipient Syn3 to promote uptake of the virus into tumor tissue.³⁴ A phase I trial demonstrated detectable levels of urinary IFN- α and no significant toxicity. A subsequent phase II study randomly assigned 40 patients with BCG-unresponsive NMIBC to low and high-dose nadofaragene.³⁵ Fourteen patients (35%) were free of high-grade recurrence at 12 months (50% for patients with papillary tumors and 30% for CIS). A phase III trial reported an overall CR rate of 59.6% at 3 months, which decreased to 30.5% at 12 months.³⁶ The CR rate was more favorable for papillary disease compared with CIS at 3 months (72.9% and 53.4%, respectively) and 12 months (43.8% and 24.3%, respectively). All patients underwent a mandatory re-biopsy after 12 months, indicating that the endpoint has been defined more stringently here than in some of the other similar trials. While this enhances the rigor of the study, the FDA does not require it for drug approval, so its use in clinical trials remains at the discretion of the study team. Nadofaragene has a favorable toxicity profile, with 4% of patients experiencing grade 3 and no patients suffering grade 4–5 treatment-related adverse events.

CG0070 is a conditionally replicating oncolytic adenovirus that expresses granulocyte-monocyte colony-stimulating factor (GM-CSF).³⁷ Viral replication and GM-CSF expression are directly and indirectly under the control of the E2F-1 promoter, which is active only in tumors with alterations in the retinoblastoma pathway. It is typically co-administered with a permeabilizing agent [0.1% dodecyl maltoside (DDM)] to allow it to penetrate the plasma membrane. CG0070 has been tested in a single-arm, phase II trial in patients with BCG-unresponsive CIS with/without papillary tumor.³⁸

The agent was administered weekly for a 6-week induction course, followed by maintenance dosing at 6, 12, and 18 months. The CR rate at 12 months in 61 patients was 30% (27% in CIS and 38% in pure Ta/T1).³⁹ Ten patients underwent cystectomy, of whom six had muscle invasive bladder cancer. Most of the adverse events were related to lower urinary tract symptoms, flu-like symptoms, and fatigue. An additional study looking at combination therapy with CG007 and pembrolizumab for BCG-unresponsive CIS is currently recruiting (NCT04387461).

BC-819 is a plasmid encoding the diphtheria toxin administered intravesically with polyethyleneimine, a cationic membrane permeabilizer.⁴⁰ The plasmid encodes the diphtheria toxin under the control of the H19 promoter sequence, an oncofetal transcription factor upregulated in urothelial carcinoma. A phase II marker lesion trial was conducted in patients with intermediate-risk disease only (no high-grade or CIS) who had recurrent or persistent disease after at least one course of any intravesical therapy.⁴¹ 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 and clinical development of this agent has been put on hold.

Targeted therapy

Oportuzumab monatox is a recombinant protein composed of humanized anti-EpCAM antibody fused to *Pseudomonas* exotoxin A.⁴² Binding of this fusion protein to cell surface EpCAM leads to internalization of the *Pseudomonas* exotoxin by receptor-mediated endocytosis, and the toxin causes arrest of protein synthesis.⁴³ Tumor EpCAM positivity has been a consistent inclusion criterion for enrolment in clinical trials. In a phase II study with EpCAM-expressing CIS, most of which was BCG-refractory, 40% of patients obtained a CR and 16% remained disease-free after 18–25 months follow-up.⁴⁴ Results from a single-arm, phase III FDA registration trial in patients with BCG-unresponsive NMIBC were reported in a company business report and at the Bladder Cancer Advocacy Network (BCAN) Think Tank 2021.⁴⁵ Oportuzumab 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 in CIS patients was 39% at 3 months and 15% at 12 months. The agent was well tolerated.

Photodynamic therapy

Photodynamic therapy (PDT) uses light energy to eradicate malignant urothelial cells. An intravesical photosensitizing agent is administered, followed by insertion of a fiber through the urethra into the bladder to transmit light from an external source. Early efforts with PDT failed due to local toxicity of non-specific photosensitizers.⁴⁶ Next-generation photosensitizing agents investigated in bladder cancer include the porphyrin hexaminolevulinic acid and ruthenium-based TLD1433.⁴⁷ These agents are preferentially taken up by malignant cells and form reactive oxygen species when activated by the appropriate wavelength of light. Bader *et al.*⁴⁸ tested PDT with hexaminolevulinic acid 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 the adequacy or nature of recurrence. Twelve per cent of patients were tumor free at 21 months. A phase I study for TLD1433 has been completed and a larger phase II trial in the BCG-unresponsive setting is underway (NCT03945162).

Novel therapies for BCG-exposed high-risk NMIBC

Clinical trial activity has also accelerated in the past several years in the BCG-exposed disease state due, at least in part, to its clear delineation from BCG-unresponsive high-risk NMIBC. Furthermore, as the standard trial design in the BCG-unresponsive setting requires only a single-arm trial, drug efficacy can potentially be validated in comparative trials in patients with BCG-exposed NMIBC. This is happening, for example, with systemic immune checkpoint blockade (NCT04149574 and NCT03711032). The standard treatment for patients with BCG-exposed high-risk NMIBC is further intravesical BCG. The established trial design therefore randomly assigns patients to additional BCG *versus* BCG plus a novel therapy.

Novel therapies for BCG-naïve NMIBC

Intravesical BCG is the standard first-line therapy for both intermediate and high-risk NMIBC. Patients who have not yet received BCG are considered BCG-naïve. Drug development in this setting typically requires randomization to BCG *versus* BCG plus a novel therapy. Other trials compare novel strains of BCG with standard

BCG. A summary of active phase II/III trials which have not yet been reported is provided in Table 3.

Intravesical chemoablation

Mitomycin has been investigated for its ablative effect potentially to replace transurethral resection of bladder tumor (TURBT) in low-grade NMIBC. The CALIBER study was a phase II feasibility study which randomly assigned patients to four once-weekly mitomycin treatments *versus* TURBT. The CR rate at 3 months was 37.0% in the chemoablation and 80.8% in the surgical arm.⁴⁹ The authors concluded that this concept was not worth pursuing in a larger phase III trial. However, investigators in Denmark have initiated the phase III DaBlaCa13 study (NCT03348969) that will test three instillations of mitomycin per week over 2 weeks before TURBT *versus* standard adjuvant mitomycin after TURBT in patients with recurrent high and low-grade Ta bladder tumors. Racioppi *et al.*⁵⁰ used the same regimen as an alternative to TURBT for recurrences measuring <1 cm in intermediate-risk NMIBC and found a CR rate of 62% at 39 months. UGN-102 is a novel thermosensitive hydrogel formulation recently studied as an ablative agent as an alternative to TURBT in low grade NMIBC with CR rates of 86–100% at 2–4 weeks post instillation.⁵¹ The phase II OPTIMA II trial, testing six weekly instillations of UGN-102 in 63 patients with low-grade Ta tumor, found a 65% CR at 3 months, and 72.5% of these patients maintained this CR for 12 months.⁵²

Fibroblast growth factor receptor inhibitor

Fibroblast growth factor receptor (FGFR) is a family of four cell-surface tyrosine kinase receptors (FGFR1–4). Erdafitinib, an FGFR inhibitor is FDA approved for use in platinum-refractory locally advanced and metastatic urothelial cancer with specific FGFR2 and FGFR3 alterations. Low grade papillary NMIBC harbors FGFR3 mutations in up to 75% of tumors, with a rapid drop off in frequency to 15–20% in CIS, high-grade T1 and muscle-invasive tumors.⁵³ These findings make FGFR a particularly attractive target in low grade NMIBC. A currently accruing phase II trial will evaluate 4–6 weeks of oral pemigatinib in low and intermediate-risk NMIBC patients prior to TURBT (NCT03914794). The primary endpoint is complete response identified at the time of TURBT. Another phase II trial is

comparing erdafitinib with investigator's choice intravesical chemotherapy in high-risk BCG-exposed or BCG-unresponsive NMIBC patients, whose tumors contain an FGFR alteration (NCT04172675). The most common side effect of this drug class is hyperphosphemia which required serum monitoring and sometimes dose reduction. Skin and nail complications are common, and the grade 3–4 treatment-related adverse event rate was 67% in metastatic bladder cancer trials, suggesting that tolerability in early stage disease will be challenging.⁵⁴ An intravesically administered FGFR inhibitor would be ideal for these patients in order to reduce toxicity.

BCG strains and priming strategy

BCG, as a live organism grown in culture, has evolved over time in different laboratories to generate numerous genetic strains. It is conceivable that different strains could elicit different responses in patients, leading to variable efficacy and toxicity. A prospective randomized trial from Bern has sparked interest in this topic, as the investigators showed clearly superior outcomes using the Connaught strain compared with the TICE strain.⁵⁵ In that trial, however, patients were treated with induction BCG only. Large retrospective studies have failed to confirm differences between strains and a systematic review by Boehm *et al.* found no differences between the Tokyo, TICE and Pasteur BCG strains with respect to recurrence rate.^{56–59} The SWOG phase III RCT S1602 completed accrual in 2021. It has compared the Tokyo-172 and TICE strains.⁶⁰ In a third arm, the Tokyo-172 strain was tested with pre-treatment intradermal BCG vaccination. Mouse models have suggested that this type of priming with BCG improves the immune response to intravesical BCG. Clinical evidence suggests also that patients with prior BCG vaccination have better outcomes with BCG therapy.⁶¹

Recombinant BCG

BCG has been genetically modified to make recombinant forms with improved efficacy and reduced adverse effect profile. Most of these agents have been developed primarily to improve BCG in the context of vaccination for prevention of tuberculosis. However, the same modifications could potentially enhance its activity in NMIBC treatment. Recombinant BCG is a promising prospect in NMIBC management and clinical trials will help to establish its role in the future.

Table 3. Ongoing clinical trials in novel agents for BCG-naïve NMIBC (phase II or later).

Immunotherapy					
Agent	Study	Study design	Inclusion criteria	Mechanism	Outcome
Tokyo 172	NCT03091660 (S1602)	Phase III 3 arm RCT 1. BCG TICE 2. BCG Tokyo strain 3. BCG Tokyo strain with intradermal vaccination	High-grade Ta, T1, CIS	As above	Time to high-grade recurrence
Pembrolizumab	NCT03504163	Phase II single arm	High-grade T1	PD-1 inhibitor	CR rate
Pembrolizumab + BCG	NCT03711032 (KEYNOTE- 676)	Phase III RCT BCG +/- pembrolizumab	2 cohorts: BCG-naïve and BCG-unresponsive	PD-1 inhibitor	CR rate
Durvalumab	NCT03528694	Phase III RCT BCG +/- durvalumab	High-risk NMIBC	PD-L1 inhibitor	CR rate
N-803	NCT02138734	Phase Ib/Ib BCG +/-ALT-803	High-risk NMIBC	IL-15 Superagonist	CR rate
Sasanlimab	NCT04165317 (CREST)	Phase III 3 arm RCT 1 sasanlimab + BCG induction/maintenance 2 sasanlimab + BCG induction only 3 BCG induction/maintenance	High-risk NMIBC	PD-1 inhibitor	CR rate
Recombinant BCG					
VPM1002BC	NCT02371447	Phase II RCT recombinant BCG: VPM1002 versus BCG post TUBRT	NMIBC	Urease C replaced with listeriolysin from <i>Listeria monocytogenes</i>	Response rate
Cytotoxic therapy					
Mitomycin	NCT03348969	Phase III RCT mitomycin 3x weekly for 2 weeks versus TURBT + adjuvant mitomycin	Ta NMIBC		CR within 2 years
Mitomycin	NCT02070120 (CALIBER)	Phase II RCT 4-weekly mitomycin versus TURBT + adjuvant mitomycin	Ta NMIBC		CR at 3 months
Liposomal paclitaxel	NCT03081858	Phase I/IIa single arm	Ta NMIBC	Paclitaxel incorporated into micelles	Safety
Neoadjuvant mitomycin	NCT03058757	Phase II neoadjuvant mitomycin versus placebo	NMIBC		Recurrence-free survival
Hyaluronate + mitomycin	2016-003813-92	Phase II RCT mitomycin +/-hyaluronate	Low-risk NMIBC	Glycosaminoglycan	

(continued)

Table 3. (continued)

Immunotherapy					
Agent	Study	Study design	Inclusion criteria	Mechanism	Outcome
Gemcitabine + docetaxel	NCT04386746	Phase II trial	Intermediate and high-risk NMIBC		CR at 3 months
Chemohyperthermia (HIVEC)	2016-001186-85	Phase II trial TURBT + HIVEC versus TURBT + BCG	High-risk NMIBC		Disease-free survival at 24 months
Encapsulated rapamycin	NCT04375813	Phase II placebo-controlled trial	BCG-naïve NMIBC	mTOR inhibitor	Recurrence-free survival
Mitomycin C depot	NCT04688931	Phase III RCT	Intermediate-risk NMIBC with CR at 3 months post TURBT	Mitomycin C administered as depot gel	Disease-free survival
Other					
Pemigatinib	NCT03914794	Phase II single-arm trial	Low and intermediate-risk NMIBC	Fibroblast growth factor receptor inhibitor	CR rate

BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; CR, complete response; NMIBC, non-muscle invasive bladder cancer; RCT, randomized controlled trial; TURBT, transurethral resection of bladder tumor.

VPM1002 is a recombinant BCG in which the urease C gene has been replaced by the listeriolyisin encoding gene from *Listeria monocytogenes*. This modifies the phagosome membrane, increasing the release of antigen into the cytosol, which in turn promotes antigen presentation and T-cell response. This enhances phagocytosis and the inflammatory reaction. A phase I study demonstrated the safety of this agent and a phase II (NCT023714470) study is now underway.

Other recombinant BCG strains are still in pre-clinical testing. rBCG-S1P expresses a detoxified S1 subunit of pertussis.⁶² This recombinant form exhibits a stronger T-cell response to pertussis in mice and an improved anti-tumor effect in a murine orthotopic bladder cancer model. *In vitro* studies using human white blood cells demonstrated an enhanced inflammatory response to rBCG-S1P compared with wild type BCG. The anti-tumor effect was also improved *in vitro*.⁶³

Cho *et al.*⁶⁴ have developed a BCG with resistance to anti-microbial peptides. Bladder cancer cells treated *in vitro* with this recombinant BCG demonstrated higher internalization and increased release of anti-tumor cytokines.

Virus-based therapy

Oncolytic viruses are also being tested in the BCG-naïve setting. These are not only capable of replicating and destroying tumor cells, but also inducing a host tumoricidal immune response. Coxsackie virus is an enterovirus which is being investigated in phase I and phase II trials. After internalization of the virus by Intercellular Adhesion Molecule 1 (ICAM-1) receptors on bladder cancer cells, the virus can directly lyse the cells and induce an immune reaction which can potentially provide lasting protective immunity in the bladder.⁶⁵ This response may be enhanced when combined with mitomycin.

Immunotherapy

The response rates to immune checkpoint inhibition have been modest in patients with BCG-unresponsive high-risk NMIBC. Multiple prospective randomized phase II trials are assessing whether first-line combination of BCG with immune checkpoint inhibition can improve the response rate and the durability of response over induction and maintenance BCG alone. Furthermore, these trials are testing whether the addition of immune checkpoint blockade can

make maintenance BCG therapy unnecessary, so that patients require only induction BCG, thereby potentially limiting the local bladder toxicity, albeit at the expense of an increased risk of systemic toxicity.

Conclusions

A clear definition of NMIBC disease states has led to a resurgence of clinical trial activity in NMIBC, with numerous novel agents under study across the disease spectrum. Many recent clinical trials have focused on BCG-unresponsive high-risk NMIBC in which the unmet need is greatest and the path towards FDA registration most established, but novel therapies are also migrating into earlier disease states. One key paradigm shift has been the introduction of systemic therapy for NMIBC. Nonetheless, BCG remains the most effective agent in our armamentarium, more than 40 years after its introduction. Time will tell if ongoing combination trials can enhance the efficacy of BCG and alter the current first and second-line treatment algorithms.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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