

Management of NMIBC during BCG shortage and COVID-19

Nikhil Mayor, Academic Foundation Doctor;¹ Christian Fankhauser, Senior Oncology Fellow;² Vijay Sangar, Consultant Urologist;² Hugh Mostafid, Consultant Urologist¹

1. Stokes Centre for Urology, Royal Surrey NHS Foundation Trust, Guildford; 2. Department of Urology, The Christie NHS Foundation Trust, Manchester

Shortages of *Bacille Calmette-Guérin* (BCG) have implications for the management of patients with non-muscle-invasive bladder cancers. Further complications come as a result of COVID-19 for which BCG also shows some promising prospects.

Bladder cancer is the ninth commonest cause of cancer death in the UK, accounting for more than 5000 deaths per year.¹ Around 80% of new cases are non-muscle-invasive bladder cancers (NMIBC) of which approximately 20% carry a high risk of recurrence or progression to muscle-invasive disease (MIBC).²

The current gold standard for management of NMIBC is transurethral resection of bladder tumour (TURBT) followed by intravesical instillation of *Bacille Calmette-Guérin* (BCG) in intermediate- to high-risk tumours. In recent times, several obstacles have arisen that have limited the use of BCG therapy, including shortage of BCG supply and the impact of the current COVID-19 pandemic.

This review provides an update on the use of BCG therapy in NMIBC patients, including recommendations on the use of BCG during times of shortage and COVID-19.

Methods

A search of MEDLINE using combinations of key words 'BCG',



The intravesical instillation of *Bacille Calmette-Guérin* (BCG) is an important measure in the treatment of intermediate- to high-risk tumours in non-muscle-invasive bladder cancers. However, recent shortages of BCG mean that alternative treatment options should also be considered

'immunotherapy', 'intravesical therapy', 'bladder cancer', 'malignancy', and 'neoplasm' for articles published between 1 January 2015 and 12 May 2020 was performed. Non-English literature, case reports, letters, and animal studies were excluded.

Response to BCG BCG strains

Intravesical instillation of BCG has been used in the management of bladder cancer for over 40 years. Despite this, many unknowns still exist regarding its mechanism.

BCG is a live attenuated strain of *Mycobacterium bovis* that is used as a vaccine against tuberculosis. However, when the strain is instilled into the bladder, a robust immune response

leading to adaptive immunity and antitumour activity can be observed.³

Various commercialised substrains of BCG have been produced that vary genetically, leading to immunogenic and phenotypical differences. Whether the substrains differ with regard to oncological outcomes is yet to be ascertained, with diverging results in the limited published literature.^{4,5} However, an ongoing randomised trial comparing the substrains (NCT03091660) as well as an early phase trial of a genetically modified strain (known as VPM1002BC) will shortly add to the evidence base.⁶

Treatment stratified by risk groups

The mainstay of BCG use is in its role as induction and subsequent maintenance therapy for NMIBC after

TURBT, with an intermediate to high risk for recurrence or progression.⁷

Risk factors that determine whether a patient has an intermediate or high risk for recurrence and progression include higher stage or grade, previous NMIBC recurrence,

larger tumour size, and greater number of tumours, as well as the presence of carcinoma *in situ* (CIS).⁸

In patients with high risk NMIBC, the standard of care represents one to three years of BCG therapy or a radical cystectomy, whereas in patients with

intermediate risk the standard of care includes a six-dose course of intravesical mitomycin C (MMC) as per NICE guidelines.⁷ The European Association of Urology (EAU) NMIBC panel suggest one year of either MMC or BCG for the intermediate risk group.⁹

Side-effect	Management option
Non-bacterial or chemical cystitis	<ul style="list-style-type: none"> • Oxybutynin, phenazopyridine, propantheline bromide, or anti-inflammatory agents (NSAIDs) • Consider postponement of intravesical therapy and subsequent dose reductions if cystitis persists beyond 48 hours • For prolonged BCG cystitis, consider use of a quinolone antibiotic
Gross haematuria	<ul style="list-style-type: none"> • Perform urine culture to exclude haemorrhagic cystitis • Suspend instillations until urine clears • Catheterisation and bladder irrigation for clots may be required
Contracted bladder	<ul style="list-style-type: none"> • Suspend instillations until resolution of symptoms • Hydrodistention • Cystectomy may be required in some instances
Ureteral obstruction	<ul style="list-style-type: none"> • Usually temporary and self-limited • Exclude presence of CIS or muscle-invasive (T2) bladder cancer • Percutaneous drainage or stenting of the kidney may be required
Symptomatic granulomatous prostatitis	<ul style="list-style-type: none"> • High-dose fluoroquinolones • Isoniazid and rifampicin for 3 months, plus quinolones and steroids • Suspension of intravesical therapy
Epididymo-orchitis	<ul style="list-style-type: none"> • High-dose fluoroquinolones • Isoniazid and rifampicin for 3 months • Suspension of intravesical therapy • Orchidectomy if severe and persistent
General malaise, fever	<ul style="list-style-type: none"> • Generally resolve within 48 hours with or without antipyretics
Persistent high-grade fever (>38.5 °C for >48 h)	<ul style="list-style-type: none"> • Permanent discontinuation of BCG instillations • Immediate evaluation • Prompt treatment with two or more antimicrobial agents (eg, fluoroquinolones, isoniazid, rifampicin) while diagnostic evaluation, including cultures, is conducted • Consultation with an infectious diseases specialist
Systemic BCG reactions	<p><i>Prevention</i></p> <ul style="list-style-type: none"> • Initiate BCG at least 2 weeks post-TURBT (if no signs and symptoms of haematuria) <p><i>Management</i></p> <ul style="list-style-type: none"> • Cessation of BCG • High-dose fluoroquinolones, isoniazid, rifampicin, and ethambutol daily for 6 months • Early, high-dose corticosteroids as long as symptoms persist • Consider an empirical non-specific antibiotic to treat Gram-negative bacteria and/or <i>Enterococcus</i>
Allergic reactions	<ul style="list-style-type: none"> • Antihistamines and NSAIDs • Consider suspension or discontinuation of BCG instillations • Consider isoniazid and rifampicin plus corticosteroids for persistent symptoms

Table 1. Recommendations for the management of intravesical therapy-related adverse events. Adapted from the International Bladder Cancer Group¹⁰

BCG side-effects, refractory disease and failure

The side-effects of BCG can vary from self-limiting, cystitis-type symptoms (experienced in the vast majority of patients) to severe infectious complications and hypersensitivity reactions (see Table 1).^{8,9,10} Such events may lead to delay or even cessation of BCG instillations; this is known as BCG intolerance and can be associated with inferior cancer-specific outcomes.

In the past, tumour recurrence after initiation of BCG therapy was known simply as BCG failure but it is now recognised that this covered two distinct subgroups of patients with different outcomes: disease persistence or progression between induction and one maintenance course is called BCG refractory disease; whereas reappearance of a tumour after one maintenance cycle is termed BCG relapse.

In BCG refractory disease, radical cystectomy without neoadjuvant chemotherapy and limited lymph node dissection is the standard of care; whereas in BCG relapse, particularly after many years, re-challenge with a further induction course of BCG may be reasonable in selected cases.

In patients unwilling to undergo cystectomy or deemed unfit for surgery (as a result of significant comorbidities, frailty or anaesthetic risk) several bladder-preserving approaches are under investigation, including maintenance therapy with intravesical chemotherapy, device-assisted instillation, intravesical and systemic immune checkpoint inhibitors,¹¹ and most recently adenoviral therapy.¹²

Treatment in times of BCG shortage

The closure of BCG production plants, reduction of production, and the withdrawal of the BCG Connaught strain manufactured by Sanofi Pasteur has led to a sustained worldwide shortage of BCG. Given the

methodological complexity and high demands of BCG production, future shortages are to be expected.

In times of BCG shortage, we recommend that urologists contact their local pharmacist or BCG supplier to consider alternative BCG strains or sterile splitting of BCG doses. Splitting BCG doses, though potentially logistically difficult, may be a viable alternative – but a one-third dose is likely the minimum required to maintain clinical effectiveness.¹³

It should be noted that reducing the number of instillations appears to be suboptimal. A multicentre phase III randomised-controlled trial (NIMBUS) assessing non-inferiority of reduced number of instillations versus standard of care was recently halted mid-recruitment after an interim safety analysis determined inferiority of the reduced schedule arm.¹⁴

Limited evidence exists for the use of other intravesical agents such as epirubicin or gemcitabine, though MMC is the most extensively investigated alternative and has the additional benefit of a reduced side effect profile in comparison to BCG.¹⁵

In the complete absence of BCG, consideration should be given to MMC with chemohyperthermia or electromotive drug administration (EMDA) where available. Hyperthermia potentiates the effect of chemotherapeutic agents and local radiofrequency-induced hyperthermia can be utilised for intravesical chemotherapy with MMC. EMDA uses a grounding pad on the anterior abdominal wall and an intravesical electrode applying a current causing MMC to be transported across the bladder urothelium, leading to deeper tissue penetration.¹¹ Nevertheless, high-risk NMIBC can be difficult to manage, and in times of BCG shortage upfront cystectomy may be the most sensible option.

Treatment in times of COVID-19

The COVID-19 pandemic presents an altogether new challenge in managing

NMIBC patients as application of BCG might be delayed. Furthermore, many patients with bladder cancer share risk factors for adverse outcomes after COVID-19 infection.¹⁶ Minimising these patients' risk of acquiring COVID-19 while maintaining BCG therapy is therefore of utmost importance. Strategies to reduce patient contact must be enforced with the construction of dedicated care pathways to minimise hospital visits.

A number of vaccines against COVID-19 have been approved by regulatory bodies across the globe with many more in development, though their impact has yet to be felt. Early epidemiological data suggest that vaccination with BCG may have a role to play in the COVID-19 pandemic.¹⁷ Since the vaccine has shown protective effects against other respiratory tract infections (for example, respiratory syncytial virus),¹⁸ it has been theorised that BCG vaccination might be a potent preventive measure against COVID-19 infection and may reduce disease severity. The mechanism by which this may occur remains under active investigation, but it is likely due to long-term activation and reprogramming of innate immune cells (so-called 'trained immunity').¹⁹

While observational studies have shown that countries with routine BCG vaccination programs have lower reported cases and deaths from COVID-19, such studies are prone to significant bias and require validation. Indeed, there are already more than ten randomised controlled trials recruiting internationally to assess the impact of BCG on transmission and disease severity in both patients and healthcare workers (summarised in Table 2).

The decades of previous experience in inoculating patients with the BCG vaccine with extremely low side-effect rates, as well as its low cost and almost global availability, make it an ideal interim measure for use in preventing COVID-19 should the RCTs provide encouraging outcomes.

Clinical trial number	Country	Intervention	Study type	Placebo	Population	Number of participants
NCT04379336	South Africa	BCG revaccination	RCT	Y	Health care workers	500
NCT04328441	Netherlands	BCG vaccine	RCT	Y	Health care workers	1500
NCT04417335	Netherlands	BCG vaccine	RCT	Y	Elderly (>60 years old)	2014
NCT04350931						
	Egypt	BCG vaccine	RCT	Y	Healthcare workers	900
NCT04362124	Columbia	BCG vaccine	RCT	Y	Healthcare workers	1000
NCT04347876	Egypt	-	Case-control	-	Any patient with proven COVID-19	100
NCT04475302	India	BCG vaccine	Interventional	N	Elderly (60–80 years old)	2175
NCT04461379	Mexico	BCG vaccine	RCT	Y	Healthcare workers	908
NCT04327206	Australia	BCG vaccine	RCT	Y	Healthcare workers	10,078
NCT04369794	Brazil	BCG vaccine	RCT	Y	Patients with proven COVID-19 (>18 years old)	1000
NCT04414267	Greece	BCG vaccine	RCT	Y	Elderly (>50 years old)	900
NCT04373291	Denmark	BCG vaccine	RCT	Y	Healthcare workers	1500
NCT04384614	Tunisia	BCG vaccine	Cross-sectional	-	Patients with COVID-19 and those who have been in contact with COVID-19	400
NCT04384549	France	BCG vaccine	RCT	Y	Healthcare workers	1120
NCT04348370	USA	BCG vaccine	RCT	Y	Healthcare workers	1800
NCT04439045	Canada	VPM1002	RCT	Y	Healthcare workers	3626
NCT04387409	Germany	VPM1002	RCT	Y	Health care worker	1200
NCT04435379	Germany	VPM1002	RCT	Y	Elderly (>60 years old)	2038

Table 2. Ongoing trials of BCG in COVID-19

However, in the absence of direct evidence, the WHO (World Health Organization) does not yet recommend BCG in the prevention of COVID-19, meaning that social distancing and/or local or national lockdown measures still represent the mainstay of prevention while we await the impact of the COVID-19 vaccination programme. This certainly holds true for NMIBC patients, where multiple hospital attendances for intravesical BCG instillation may not be feasible or sensible, meaning that radical cystectomy may be necessary only in the high-risk groups.

Conclusion

Patients with NMIBC can carry a substantial risk of recurrence and progression to advanced disease. Intravesical BCG is an effective, bladder-preserving treatment option that should be offered to patients with intermediate- to high-risk NMIBC.

Due to the various factors currently affecting the supply of BCG, shortages are likely to represent a recurring issue; however, several alternative treatment options can be considered during these periods. During times of high local COVID-19 prevalence, BCG

treatment might not be possible as many patients with NMIBC are at high risk of suffering detrimental COVID-19 outcomes, or have had treatment delayed. Accordingly, pathways to maintain BCG therapy with minimal risk in contracting COVID-19 should be developed.

Finally, early indicators suggest that coverage with BCG vaccination may be a promising preventative strategy in tackling COVID-19; however, outcomes of randomised controlled trials will shed further light on this theory.

Declaration of interests: none declared.

References

1. Cancer Research UK. Bladder cancer statistics (www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer#heading-One; accessed 22 December 2020).
2. Mostafid H, Bryan RT, Rees J. Diagnosis and treatment of non-muscle-invasive bladder cancer. *Trends in Urology and Men's Health* 2015;6(2):23–7.
3. Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. *Nat Rev Urol* 2018;15:615–25.
4. Boehm BE, Cornell JE, Wang H, *et al.* Efficacy of bacillus Calmette-Guérin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis. *J Urol* 2017;198:503–10.
5. Quan Y, Jeong CW, Kwak C, *et al.* Dose, duration and strain of bacillus Calmette-Guérin in the treatment of nonmuscle invasive bladder cancer. *Medicine (Baltimore)* 2017;96:e8300.
6. Rentsch CA, Bosshard P, Mayor G, *et al.* Results of the phase I open label clinical trial SAKK 06/14 assessing safety of intravesical instillation of VPM1002BC, a recombinant mycobacterium Bacillus Calmette Guérin (BCG), in patients with non-muscle invasive bladder cancer and previous failure of conventional BCG therapy. *Oncoimmunology* 2020;9(1):1748981.
7. National Institute for Health and Care Excellence (NICE). Bladder cancer: diagnosis and management. NICE guideline [NG2]. Recommendations (www.nice.org.uk/guidance/ng2/chapter/1-Recommendations; accessed 22 December 2020).
8. Sylvester RJ, Van Der Meijden APM, Oosterlinck W, *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49(3):466–77.
9. Babjuk M, Burger E, Compérat P, *et al.* European Association of Urology Guidelines: Non-muscle-invasive Bladder Cancer (<https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer>; accessed 22 December 2020).
10. Witjes JA, Palou J, Soloway M, *et al.* Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy-Associated Adverse Events. *European Urology Supplements* 2008;7(10):667–74.
11. Kamat AM, Colombel M, Sundi D, *et al.* BCG-unresponsive non-muscle-invasive bladder cancer: Recommendations from the IBCG. *Nat Rev Urol* 2017;14:244–55.
12. 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* 2020;22:107–17.
13. Fankhauser CD, Teoh JYC, Mostafid H. Treatment options and results of adjuvant treatment in nonmuscle-invasive bladder cancer (NMIBC) during the Bacillus Calmette-Guérin shortage. *Curr Opin Urol* 2020;30(3):365–9.
14. Grimm MO, van der Heijden AG, Colombel M, *et al.* Treatment of High-grade Non-muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial 'NIMBUS'. *Eur Urol* 2020;78:690–8.
15. Siracusano S, Silvestri T, Bassi S, *et al.* Health-related quality of life after BCG or MMC induction for non-muscle invasive bladder cancer. *Can J Urol* 2018;25(5):9480–5.
16. Knights H, Mayor N, Millar K, *et al.* Characteristics and outcomes of patients with COVID-19 at a district general hospital in Surrey, United Kingdom. *Clin Med* 2020;20:e148–e153.
17. Miller A, Reandelar MJ, Fasciglione K, *et al.* Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv preprint (www.medrxiv.org/content/10.1101/2020.03.24.20042937v2; accessed 22 December 2020).
18. Bueno SM, González PA, Cautivo KM, *et al.* Protective T cell immunity against respiratory syncytial virus is efficiently induced by recombinant BCG. *Proc Natl Acad Sci USA* 2008;105(52):20822–7.
19. Redelman-Sidi G. Could BCG be used to protect against COVID-19? *Nat Rev Urol* 2020;17:316–7.