AUA Update Series 2021
Lesson 2 Volume 40

Intravesical BCG Therapy for Bladder Cancer*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to state the utility of intravesical bacillus Calmette-Guérin for treatment of non-muscle invasive bladder cancer and contemporary management of high risk non-muscle invasive bladder cancer. The participant will also be able to describe the bacillus Calmette-Guérin shortage and conservation strategies such as patient prioritization plus use of different bacillus Calmette-Guérin strains.

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***This AUA Update addresses the Core Curriculum topic of Oncology - Adult and the American Board of Urology Module on Oncology, Urinary Diversion and Adrenal.**

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Release date: January 2021

Expiration date: January 2024

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Key Words: administration, intravesical; urinary bladder neoplasms; drug therapy; survival; immunotherapy

BACKGROUND

Non-muscle invasive bladder cancer remains among the most common malignancies of the urinary tract. Intravesical bacillus Calmette-Guérin administration is the gold standard immunotherapy treatment for eradication of carcinoma in situ and for adjuvant therapy following surgical removal of papillary non-muscle invasive bladder cancer. In head-to-head clinical trials BCG outperforms intravesical chemotherapy in treating non-muscle invasive bladder cancer. Periodic episodes of BCG production shortages occur as a consequence of mass production challenges and these shortages result in substandard care for patients. Strategies to mitigate consequences of BCG shortages include prioritization of BCG for highest risk patients, split dosing BCG vials and use of BCG for induction only. Urologists should be familiar with practical application of BCG, including management of side effects. Future aims include testing alternative agents, other BCG strains and recombinant formulations of BCG.

INCIDENCE, TRENDS AND RISK FACTORS

Bladder cancer is the fourth most common cancer in men.[1, 2] In the United States approximately 80,000 new cases of bladder cancer and 17,000 deaths from bladder cancer occur each year.[2] Around 70% of people with bladder cancer are diagnosed with non-muscle invasive bladder cancer, defined as disease confined to the submucosa or lamina propria, with a median age of diagnosis of 73 years.[3, 4] Additionally, up to 70% of NMIBC recurs after initial treatment, with 10% to 20% of the recurrences being muscle invasive bladder cancer (much poorer prognosis).[5] The 5-year survival rate for patients with NMIBC is approximately 88%, which compares favorably to the less than 60% 5-year survival rate for patients with muscle invasive bladder cancer.[3, 5] Disease metastasis is uncommon for patients with NMIBC and usually indicates understaging of the primary tumor (ie muscle invasive bladder cancer that was not adequately staged).[4] Patients with bladder cancer most often present with painless gross hematuria. Less common signs/symptoms of presentation include dysuria, change in urinary frequency, urinary urgency, flank pain, pelvic pain, and palpable mass.[4, 5] Occasionally bladder cancer is detected incidentally through imaging performed for an unrelated cause; imaging findings in bladder cancer include bladder mass, clot in the bladder, hydronephrosis and pelvic lymphadenopathy. Risk factors for the development of bladder cancer include: advanced age, male gender and environment exposure to carcinogens, especially tobacco smoke.[6] Smoking at the time of bladder cancer diagnosis is associated with higher recurrence rates of NMIBC. Furthermore, smokers with muscle invasive bladder cancer are more likely to die of bladder cancer.[7] Lastly, frequent occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons has also been shown to increase risk of bladder cancer.[8]

BCG THERAPY EFFICACY

BCG is approved as adjuvant treatment of papillary Ta–T1 bladder cancer following endoscopic tumor resection and for eradication of CIS. The treatment pattern for BCG administered includes an induction course of 6 weekly instillations followed by 7 maintenance courses of 3 weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months from initial tumor resection. The maintenance courses are generally given 1 to 2 weeks following a normal cystoscopy.[9] AUA recommended basic treatment guidelines following transurethral resection of bladder tumor based on risk stratification are shown in the figure.[10] **Intravesical BCG administration reduces disease recurrence and progression.[9, 11]**

Urologists should be familiar with 2 landmark BCG studies conducted by SWOG (Southwest Oncology Group). The first study, published in 1991, compared intravesical doxorubicin against intravesical BCG for patients with NMIBC.[12] In this study patients with Ta–T1 tumors without concurrent CIS had an estimated probability of being recurrence free at 5 years of 17% for patients receiving doxorubicin and 37% for patients receiving BCG (p=0.015). For patients with CIS the complete response estimates were 37% for patients receiving doxoru-bicin and 70% for patients receiving BCG (p <0.001). The second study, SWOG-8507, compared BCG maintenance vs no maintenance.[13] This study reported a recurrence-free survival estimate of 36 months for patients receiving no maintenance compared to 77 months for patients receiving maintenance (p <0.001). Furthermore, due to a policy at that time of with-holding maintenance BCG for patients with increased side effects, most patients did not complete the maintenance regi-men (only 16% completed full maintenance regimen). It is possible that more rigorous adherence to maintenance could have resulted in an even higher improvement in recurrence-free survival.

Intravesical chemotherapy, such as mitomycin C, epirubicin and gemcitabine, have also demonstrated efficacy at prevent-ing disease relapse in NMIBC. Yet in head-to-head comparison trials BCG consistently outperforms intravesical chemother-apy for treating NMIBC.[11,12,14-17] Collectively these reports led to the current practice paradigm in which BCG induction and maintenance is the standard of care treatment for high grade and high risk NMIBC.

Intravesical chemotherapy such as mitomycin C and gemcitabine work through direct cellular cytotoxicity. Although there is some suggestion that BCG can also directly kill tumors, BCG is widely thought to mediate tumor killing through stimu-lating the body's immune system. Our understanding of BCG's mechanism of action comes from experimental rodent models. In such models, immune cells shown to contribute to BCG response include NK cells,[18] macrophages,[19] αb T cells[20] and γd T cells.[21] Furthermore, in experimental models BCG binds to the urothelial surface by binding fibronectin, which allows

ABBREVIATIONS: AUA (American Urological Association), BCG (bacillus Calmette-Guérin), CIS (carcinoma in situ), EAU (European Association of Urology), FDA (U.S. Food and Drug Administration), NMIBC (non-muscle invasive bladder cancer), PPD (purified protein derivative), TURBT (transurethral resection of bladder tumor)

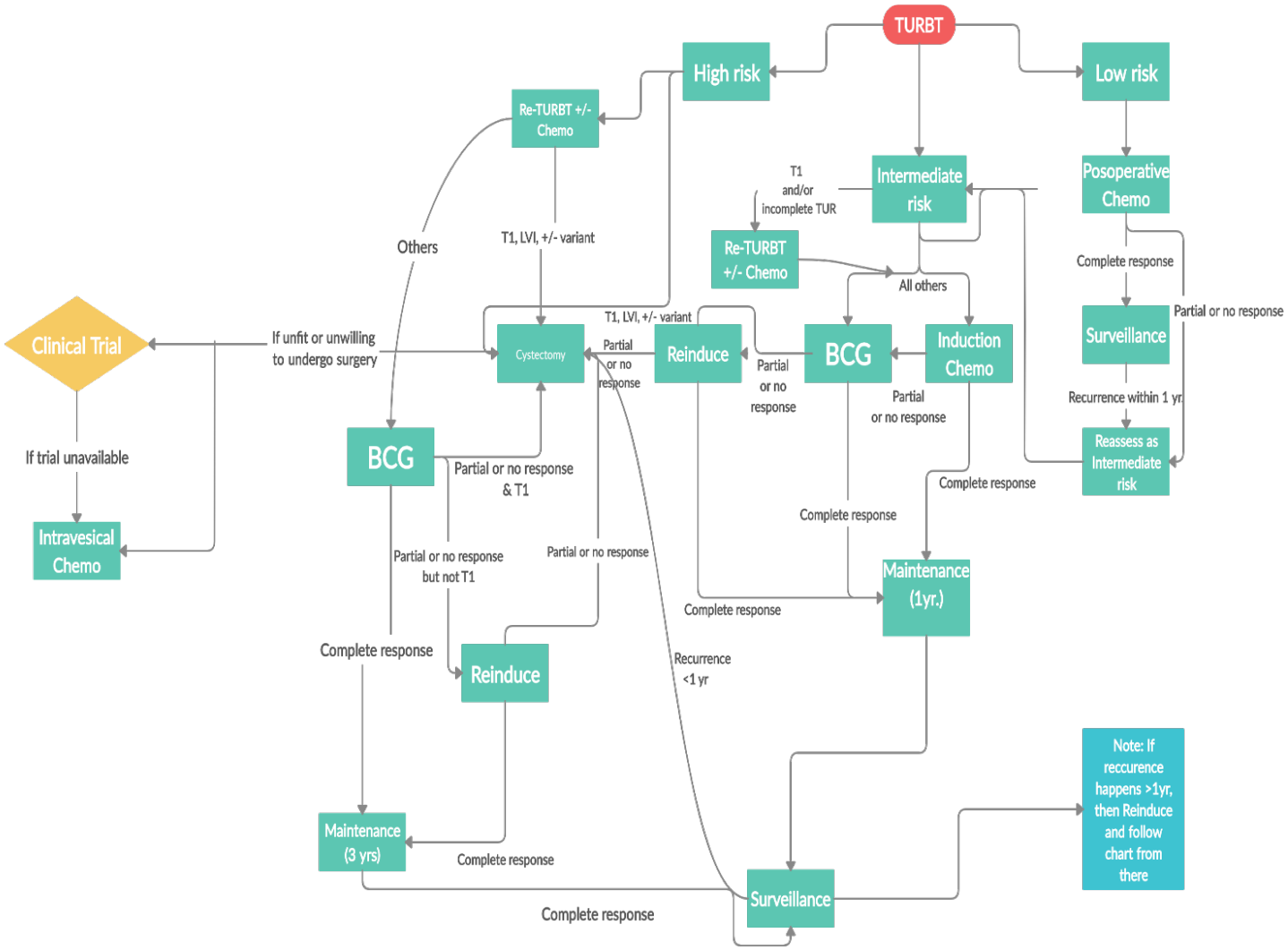

Figure. Summarized/condensed AUA NMIBC post-TURBT treatment guidelines.[10]

for its immune response against tumors.[22] Some studies also found that administration of anticoagulants that inhibit fibrin clot formation decreased BCG antitumor activity. However, a systematic review of publications addressing correlations between oral anticoagulant medications and BCG outcomes concluded that there is insufficient evidence to recommend for or against discontinuation of anticoagulant medications during BCG therapy.[23] Bladder cancer generally affects the elderly population who frequently suffer from comorbid conditions such as coronary artery disease and atrial fibrillation. Thus, it is common practice to continue anticoagulation for these high risk patients during BCG therapy.

TREATMENT GUIDELINES

The American Urological Association and the European Association of Urology provide guidelines for the treatment and management of bladder cancer based on peer-reviewed literature and expert opinion.[6,10,24] Both guidelines recommend stratification of disease risk based on probability of disease relapse and progression. **Key elements to risk stratification include tumor stage, grade, size and focality.** Additional considerations include other high risk features, including variant histology, presence of lymphovascular invasion, presence of prostatic urethral involvement and poor response to BCG.[24,25]

AUA Guidelines. AUA guidelines discuss the importance of initial diagnosis of NMIBC.[10,24] Determination of the need for BCG is based on the patient's risk of disease recurrence and progression. Thus, "at the time of each occurrence or recurrence of tumor, the clinician should assign a clinical stage and classify a patient accordingly as low, intermediate or high risk." Appendix 1 shows AUA recommended risk stratification categories for post-TURBT to help guide postoperative therapy.[10,24] BCG is not recommended for patients with low risk disease. BCG can be considered for patients with intermediate risk disease, and patients with high risk disease should be treated with induction and maintenance BCG (at 3 and 6 months, then every 6 months for 3 years).[10] Intravesical chemotherapy is another option for intermediate risk disease.

EAU guidelines. EAU guidelines also stratify patients into 3 risk groups (low, intermediate or high risk), which helps to guide treatment.[6, 26] Appendix 2 shows the EAU recommended risk stratification categories for tumor staging to help guide treatment. BCG is not recommended for low risk patients. BCG is recommended for intermediate risk patients, including induction plus maintenance for 1 year.[6, 26] Alternatively, according to EAU guidelines, intermediate risk patients could be treated with intravesical chemotherapy. High risk patients should undergo full-dose intravesical BCG therapy for 1 to 3 years and radical cystectomy can also be considered for high stage tumors.

BCG STRAINS

BCG was developed as a vaccine to prevent tuberculosis. The initial strain of *Mycobacterium bovis* was obtained from a cow infected with bovine tuberculosis. In the laboratory of Calmette and Guérin in France, this strain was propagated repeatedly in order to develop an attenuated strain that could protect against subsequent tuberculosis infection. Once the vaccine was developed in the 1920s, this initial BCG strain (ie Pasteur strain) was dispersed to different countries worldwide for increased vaccine development.[27, 28] Evolution of this strain then took place across different laboratories throughout the world as BCG was grown under various and unique conditions. This evolution continued until the 1960s when a freeze lot system was put into place.[28-30] As a result of the worldwide disbursement and growth of BCG in various locations, many biologically distinct BCG strains emerged with unique genetic and immunological properties. Examples of different BCG strains are Pasteur, Connaught, Tokyo, TICE, Armond-Frappier, Danish and Glaxo.[28, 31] **Because of their genetic modifications, the different BCG strains differ biologically in terms of reactogenicity (ie production of side effects of symptoms) and immunogenicity (ie induction of humoral or cell mediated measurable immune responses).[16, 31]** The original Pasteur strain has been so heavily altered over the years that it is least used due to its high reactogenicity.[31] Some strains are found to stimulate immune responses better than others. For example, in murine models TICE and Pasteur strains secrete more heat shock proteins than the Tokyo strain.[32]

It is unclear if the biological differences of BCG strains translate into differences in efficacy (either for tuberculosis prevention or for bladder cancer treatment). Experimental murine models have shown that BCG strains vary in their virulence and efficacy for tuberculosis protection.[33] Analysis of strain efficacy has gained increased importance recently due to global BCG shortages (see below). A randomized trial of Connaught vs TICE BCG among 142 patients demonstrated a significant difference in recurrence-free survival.[33] Five-year recurrence-free survival was 74% for patients treated with Connaught strain compared to 48% for patients treated with TICE BCG (p=0.01). However, this study was criticized because of the lack of maintenance BCG. Another trial compared Connaught strain vs Tokyo strain but was closed prematurely due to lack of BCG. This trial found comparable outcomes between Connaught vs Tokyo strain among 38 patients.[34] A network meta-analysis evaluated all published reports of BCG efficacy across various strains and found that all BCG strains had significant superiority over intravesical chemotherapy in preventing disease relapse, but no definitive conclusions could be reached regarding strain superiority due to lack of sufficient comparative trial data.[35] S1602 is a 3-arm randomized trial currently enrolling patients and will seek to compare the efficacy of TICE vs Tokyo-172 BCG strains.[36, 37] This study will provide the first appropriately powered study to address BCG strain efficacy and side effect differences.

BCG SHORTAGE

History and inception. Periodic production problems are the most common reason why BCG shortages occur. **BCG is an attenuated but live organism.** Growth and maintenance of BCG seed lots is susceptible to handling, equipment malfunction and environmental conditions.[38] In addition, BCG is currently marketed at a relatively inexpensive cost compared to other chemotherapies, which decreases the incentive for companies to manufacture the agent. In 2011 Sanofi Pasteur (the vaccines division of the French mutational pharmaceutical company Sanofi) suffered a setback that interrupted their BCG supply chain. This company, which manufactured the Connaught BCG strain, suffered a flood of its manufacturing facility, leading to development of unsanitary conditions such as mold, nesting birds and rusted machinery. Thereafter, Sanofi Pasteur announced a suspension of the production of their BCG Connaught strain in June 2012 and then completely ceased production in 2017.[31, 38] The 2003 Medicare Modernization Act limited generic drug costs to 6% above the Medicare average sale price. This led to lower reimbursement for pharmacies for the cost of dispersing drugs and inadequate reimbursement for pharmaceutical companies to profit from production of BCG.[39-41]

Implications for practice (workflow and coordination of patients). Periodic BCG shortages force physicians to lower the administered BCG dose, shift to less efficacious treatment options or stop BCG altogether.[41] BCG shortages result in a reduction in maintenance courses, yielding suboptimal treatment. In addition, under times of BCG shortage patients may be offered radical cystectomy more frequently as a means of controlling disease progression or metastasis, resulting in unnecessary morbidity and impact on quality of life. Estimates of the effect of BCG shortage suggest that BCG interruption is associated with a significant reduction in recurrence-free and progression-free survival. **During BCG shortages, it has been reported that 40% of patients did not complete induction BCG and maintenance therapy was not given in 60% of patients.[42]** Furthermore, the increased price of the only other available therapeutic options, such as intravesical chemotherapy, increases the financial burden on patients and health care systems.[41, 42]

AUA recommendations. In response to the BCG shortages the AUA made the following recommendations:[10, 24, 43]

1. BCG should not be used for patients with low risk disease.
2. Intravesical chemotherapy should be used as the first line option for patients with intermediate risk NMIBC. Patients with recurrent/multifocal low grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin or docetaxel instead of BCG.
3. If BCG would be administered as second line therapy for patients with intermediate risk NMIBC, an alternative intravesical chemotherapy should be used rather than BCG in the setting of this BCG shortage.

4. Patients with high risk NMIBC, high grade T1 and CIS patients receiving induction therapy should be prioritized for use of full strength BCG. If not available, these patients and other high risk patients should be given a reduced one-half to one-third dose, if feasible.
5. If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use one-third dose BCG and limit dose to 1 year.
6. In the event of BCG supply shortage, maintenance therapy should not be given, and BCG naïve patients with high risk disease should be prioritized for induction BCG.
7. If BCG is not available, a preferable alternative to BCG is mitomycin (induction and monthly maintenance up to 1 year). Other options such as gemcitabine, epirubicin, docetaxel, valrubicin or sequential gemcitabine/docetaxel or gemcitabine/mitomycin may also be considered with an induction and possible maintenance regimen.
8. Patients with high risk features (ie high grade T1 with additional risk factors such as concomitant carcinoma in situ, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents should be offered initial radical cystectomy if they are surgical candidates.

BCG organisms are very stable at room temperature, and split doses can be used for other patients receiving BCG on the same day. The AUA and Society of Urologic Oncology recommend that the BCG vial should be split when multiple patients can be treated so as to prevent drug wasting. This has generated billing issues as the Centers for Medicare and Medicaid Services did not have a policy regarding split dosage billing. A new Healthcare Common Procedure Coding System (J9030) has been approved for split dosing BCG live intravesical instillation, 1 mg. However, the AUA still recommends contacting insurance companies prior to dose splitting.[43, 44] The AUA also posted a Policy and Advocacy Brief in September 2019 to further discuss split BCG billing questions and topics.[44] Although BCG is attenuated, in most U.S. institutions it is still considered an infectious organism posing a moderate health hazard (biosafety level 2). Therefore, splitting of BCG should be done in a hood with appropriate biosafety level 2 precautions.[45, 46] Personnel delivering BCG should take appropriate biosafety level 2 precautions:

1. Appropriate personal protective equipment must be worn, including lab coats and gloves. Eye protection and face shields can also be worn, as needed.
2. All procedures that can cause infection from aerosols or splashes are performed within a biological safety cabinet.
3. An autoclave or an alternative method of decontamination is available for proper disposals.
4. A sink and eyewash station should be readily available.
5. Biohazard warning signs should be posted.

PRACTICAL CONSIDERATIONS IN BCG DELIVERY

Administration safety. While intravesical chemotherapy may be used within 24 hours after TURBT (assuming no bladder perforation), intravesical BCG should not be given immediately after TURBT. Generally, BCG is given at least 1 week or more after TURBT. In the past patients stayed in clinic during BCG instillation, laid supine and rotated (supine to prone) at specified intervals for the 2-hour duration. This practice is no longer common as rolling maneuvers are not necessary for ensuring complete contact between BCG and the uroepithelium.[47] The use of antibiotics prior to catheterization or postoperatively has not proven entirely beneficial. Although studies have shown that antibiotic use occasionally shows a modest decrease in the risk of sepsis, iatrogenic urinary tract infections and lower urinary tract symptoms, it has not been advocated widely. Carey et al[48] and Herr[49] found that BCG can even be administered with asymptomatic bacteriuria. On another note, evidence shows that minimizing fluid intake prior to BCG instillation helps to ensure maximum treatment effect by preventing dilution.[47, 48] Most practices allow patients to void at home, and patients are instructed to sanitize the toilet with bleach after voiding the BCG. Data regarding the effects of BCG on pregnancy and reproduction are lacking. BCG should not be given to pregnant women unless there are no better alternatives and requires careful consideration. Some major health systems have policies regarding sexual health. Altru Health System advises men to avoid intercourse for 48 hours after BCG treatment; men should use a condom for sex during the treatment course and for 6 weeks after final instillation.[50] Furthermore, women undergoing BCG treatment should avoid vaginal contact for 1 week after each instillation and until 6 weeks after final instillation. These practices are also mentioned by Saluja and Gilling.[51]

Purified protein derivative conversion. Intravesical BCG therapy will cause PPD conversion (from negative to positive) in up to 50% to 60% of patients.[52] BCG manufacturers recommend testing PPD tuberculin reactivity in patients needing BCG treatment prior to BCG administration. However, this is not standard practice due to low prevalence of tuberculosis in the United States. Furthermore, Kamat et al explain that a positive PPD should not exclude patients from BCG treatment.[47] **Rather, in otherwise healthy patients who are PPD positive (induration >10 mm), active tuberculosis should be ruled out because intravesical BCG is contraindicated in active tuberculosis infection.** Evaluation for active tuberculosis requires a careful history and physical examination, chest x-ray, sputum culture (if indicated by symptoms) and IFN-g release assay. Unlike a PPD test, IFN-g release assays examine reactivity to proteins specific for *Mycobacterium tuberculosis* and are not affected by prior BCG vaccination or prior intravesical BCG therapy.[53] Available IFN-g release assays include QuantiFERON®-TB Gold In-Tube test and T-SPOT®. These tests measure a patient's T cell release of IFN-g in response to *M. tuberculosis* immunodominant antigens (eg ESAT-6, CFP-10 and TB7.7).

Contraindications. Absolute contraindications for intravesical BCG administration include an active urinary tract infection, gross hematuria and recent urothelial trauma (eg traumatic catheterization). Patients undergoing antibiotic therapy may consider postponing BCG instillations due to the risk of decreasing the BCG effectiveness. Relative contraindications include patient immunosuppression. Because BCG's mechanism of action is multifactorial (see *mechanism* above) and involves components of both the innate and adaptive immune system, one should not assume that BCG would be ineffective in patients with immunosuppression. It is documented that BCG can be given to immunologically compromised patients, including patients with organ transplants, receiving systemic

chemotherapy and taking steroids.[54] However, because such patients are at higher risk for complications from sepsis, caution is advised for such patients, and a urine culture should be performed prior to each BCG instillation to rule out bacteriuria.

Managing adverse effects. **Common low grade side effects from BCG instillation include cystitis, dysuria, malaise, low grade fever, urinary frequency and urgency.** These symptoms usually resolve within 24 hours. Appendix 3 reveals genitourinary adverse effects.[55, 56] Patients should be evaluated for other signs/symptoms not typical of anticipated BCG related treatment effects. Management for these anticipated BCG induced side effects includes reassurance, nonsteroidal anti-inflammatories, Pyridium® (phenazopyridine), anticholinergics and beta-3 agonist (Myrbetriq®), among others. If these symptoms do not resolve after 24 to 48 hours, obtain a urine culture to evaluate for other bacterial infection and consider a short course of oral steroids. A short course of steroids has been shown to be effective in patients refractory to conservative methods.[55] If the patient does not respond to steroids, consider starting isoniazid treatment. Restarting BCG is possible after symptoms resolve, but patients may require a reduction of BCG dose (eg one-third or one-quarter dose). **Less common and more systemic adverse effects include reactive arthritis, BCG sepsis, granulomatous hepatitis and miliary pulmonary tuberculosis.** Appendix 3 lists some of these adverse effects and treatment guidelines.[56] If a patient has a fever >101.5F for more than 24 to 48 hours, first rule out other infectious causes. If no other identifiable cause, start isoniazid at 300 mg by mouth daily for 3 months. Anecdotally it is possible that intravesical BCG can be given while the patient is receiving isoniazid. Two studies showed that patients treated with BCG and isoniazid still had a longer time to first recurrence than epirubicin treated patients.[15, 57] Nevertheless, consultation with infectious disease is necessary before making this decision. Disseminated BCG infection is an uncommon but dangerous adverse effect of intravesical BCG therapy. BCG-osis (ie disseminated BCG) requires hospital admission, blood cultures for mycobacteria (ie acid-fast bacilli) and lung imaging. Broad-spectrum antibiotics and antituberculosis drugs (ie isoniazid, rifampin, ethambutol) should be started immediately in consultation with infectious disease physician.[55, 56] The BCG that was administered should be tested for drug susceptibleness since some mycobacteria may be resistant to certain antituberculosis medications. BCG is naturally resistant to pyrazinamide. Consider using cycloserine and intravenous steroids (eg 40 mg prednisolone intravenously daily) in severe cases.

FUTURE PERSPECTIVES

As pointed out by Bandari et al, existing economic and regulatory factors continuously affect the production and availability of biologic therapeutics.[58] They propose 5 recommendations to mitigate those factors and ensure best possible treatment availability, including 1) introducing other available substrains of BCG into clinical practice, 2) determining the optimal BCG maintenance doses and schedules, 3) introducing alternative intravesical and systemic treatment strategies for adjuvant intravesical therapy, 4) consideration of early radical cystectomy and 5) insight to policy makers. In addition, strategies to boost relevant immune responses in ways that allow much lower doses of BCG to be used should be explored.

DID YOU KNOW?

NMIBC risk factors and incidence:
- Bladder cancer is the fourth most common cancer in U.S. men, and 70% of bladder cancers are classified as NMIBC.
- Bladder cancer risk factors are age, male gender, smoking and polyaromatic compounds.

BCG efficacy:
- Eradicates CIS.
- Prevents disease relapse and progression in patients with Ta–T1.

Risk stratification:
- Primary risk stratification factors: pathological stage, grade, tumor size and focality.
- Secondary risk stratification factors: lymphovascular invasion, variant histology, prostatic involvement and poor response to BCG.

Indications for BCG therapy:
- Carcinoma in situ (also known as high grade dysplasia).
- High grade Ta–T1.

BCG strains:
- FDA approved: Connaught, TICE, Armond-Frappier.
- FDA approved and available in U.S.: TICE.

BCG properties:
- Genomics, immunogenicity and reactogenicity vary across BCG strains.
- Efficacy of BCG strains has not been tested in well controlled prospective trials.

Solutions to managing BCG shortages:
- Prioritization of existing BCG for highest risk patients.
- Split dosing and decreasing number of maintenance instillations.
- Considering alternative treatment options (eg intravesical chemotherapy or cystectomy).

Appendix 1. AUA NMIBC risk stratification[10, 24]

Low risk	Low grade solitary Ta tumor, < 3 cm Papillary urothelial neoplasm of low malignant potential
Intermediate risk	Recurrence within 1 year, low grade Ta tumor Solitary low grade Ta tumor, > 3 cm Low grade Ta, multifocal tumors High grade Ta, < 3 cm Low grade T1
High risk	High grade T1 Any recurrent high grade Ta or any high grade Ta High grade Ta, > 3 cm (or multifocal) Any carcinoma in situ Any BCG failure in high grade patient Any variant histology Any lymphovascular invasion Any high grade prostatic urethral involvement

Appendix 2. EAU NMIBC risk stratification[6, 26]

Low risk	Primary, solitary, TaG1 (PUNLMP, LG), <3 cm No CIS
Intermediate risk	Any tumors not identified as either low or high risk Essentially, any tumor between high and low risk
High risk	T1 tumors Grade 3 (high grade) tumors CIS Note: Highest risk tumors are a separate subgroup and are as follows: T1 grade 3/ high grade with concurrent bladder CIS, recurrent or large grade 3/high grade, grade 3/high grade in prostatic urethra, urothelial carcinoma with certain variant histology, lymphovascular invasion

Appendix 3. List of adverse effects associated with intravesical BCG administration[6,10,24,55,56]

	Treatment	BCG Modification
Genitourinary complications		
Cystitis	Nonsteroidal anti-inflammatories, anticholinergic drugs, antibiotics if necessary	Hold BCG until symptoms cease and antibiotics are stopped
Kidney infection	300 mg isoniazid and 600 mg rifampin daily for 3–6 months	Stop BCG
Tuberculous epididymo-orchitis	300 mg isoniazid and 600 mg rifampin daily for 3–6 months	Stop BCG
Ureteral obstruction/ hydronephrosis	300 mg isoniazid and 600 mg rifampin daily for 3–6 months Drainage for hydronephrosis	Stop BCG until hydronephrosis is resolved
Systemic complications		
BCG sepsis	300 mg isoniazid, 600 mg rifampin and 1,200 mg ethambutol daily for 3–6 months; intravenous 40 mg prednisolone initially and then oral steroids tapered gradually	Stop BCG
Granulomatous hepatitis	300 mg isoniazid, 600 mg rifampin and 1,200 mg ethambutol daily for 3–6 months	Stop BCG
Miliary pulmonary tuberculosis, interstitial pneumonitis	Combined isoniazid, ethambutol, streptomycin or rifampin for 6–12 months	Stop BCG
Reactive arthritis	Nonsteroidal anti-inflammatory drugs ± corticosteroids; methotrexate and other disease modifying drugs with isoniazid if no improvement	BCG can be resumed once symptoms are reduced; dose reduction should be considered

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Study Questions Volume 40 Lesson 2

1. A recommended management strategy during a BCG shortage is to
   a. use a non-FDA approved BCG strain
   b. prioritize full strength induction BCG for patients with high risk bladder cancer
   c. alternate weekly BCG and intravesical chemotherapy
   d. avoid induction BCG and use available BCG for maintenance

2. In a patient who has undergone TURBT of high risk NMIBC, provided there are no drug shortages, the best treatment course is a 6-week course of intravesical
   a. mitomycin C followed by monthly mitomycin C up to 1 year
   b. mitomycin C followed by monthly mitomycin C up to 9 months
   c. BCG, followed by BCG administration at 6 months and every 3 months after, if tolerated, out to 2 years
   d. BCG, followed by BCG administration at 3, 6 and 12 months, and every 6 months after, if tolerated, out to 3 years

3. In a trial comparing the use of BCG Connaught strain to BCG Pasteur strains for NMIBC treatment, patients who received the Pasteur strain had a higher incidence of urinary urgency, fever and fatigue compared to the patients receiving the Connaught strain. This finding implies that the Pasteur strain of BCG in comparison to the Connaught strain has a higher
   a. reactogenicity
   b. immunogenicity
   c. volatility
   d. instability

4. A patient experiences persistent dysuria and urinary urgency 3 days after instillation of his 6th dose of induction BCG. A urine culture is obtained and shows no growth. Workup reveals a negligible post-void residual. The next best step is
   a. treat with phenazopyridine and an antimuscarinic or beta-3 agonist
   b. treat with a short course of methylprednisolone
   c. initiate isoniazid and follow liver function tests
   d. admit patient to the hospital and consult infectious disease

5. During a BCG shortage a 67-year-old man with a history of bladder cancer who is BCG naïve is found to have a new tumor on surveillance cystoscopy. TURBT reveals a T1 high grade bladder cancer. T1 high grade bladder cancer is found on a re-resection, which includes muscle. There are 3 vials of BCG available. The next step is
   a. split the BCG vials in half and give over 6 weeks
   b. give an induction course of intravesical mitomycin C
   c. alternate intravesical BCG (full strength) and intravesical mitomycin C for 6 doses
   d. radical cystectomy

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