



Intravesical Administration of Therapeutic Medication for the Treatment of Bladder Cancer

Jointly developed with the Society of Urologic Nurses and Associates (SUNA)

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I. Statement of Purpose:

To define the performance guidance surrounding the instillation of intravesical cytotoxic, immunotherapeutic, and/or therapeutic drugs via sterile technique catheterization for patients with non-muscle invasive bladder cancer (NMIBC, urothelial carcinoma).

II. Population:

Adult Urology

III. Definition:

Intravesical therapy involves instillation of a therapeutic agent directly into the bladder via insertion of a urethral catheter.

IV. Indications:

For administration of medication directly into the bladder via catheterization utilizing sterile technique for NMIBC treatment.

V. Guidelines and Principles:

Health care personnel (MD, NP, PA, RN, LPN, or MA) performing intravesical therapy must be educated, demonstrate competency, and understand the implications of non-muscle invasive bladder cancer. (Scope of practice for health care personnel listed may vary based on state or institution). This should include associated health and safety issues regarding handling of cytotoxic, and immunotherapeutic agents; and documented competency of safe practical skills. At a minimum, each institution or office practice setting should implement an established, annual competency program to review safety work practices and guidelines regarding storage, receiving, handling/ transportation, administration, disposal, and handling a spill of hazardous drugs. (Mellinger, 2010)

VI. Immunotherapy, Cytotoxic and Therapeutic Medications Used:

- A. Intravesical Mitomycin C, Epirubicin, and Gemcitabine are cytotoxic agents that inhibit DNA synthesis in bladder cancer cells. They may be given immediately, post-transurethral resection of bladder tumor (TURBT) in absence of perforation.
- B. Sodium bicarbonate, which raises the pH of serum and urine, may be used orally or intravesically in combination with Mitomycin C to buffer urine pH to optimize therapy and decrease recurrence of bladder tumors. (Au, 2001)
- C. Intravesical Bacillus Calmette-Guérin (BCG), an immunotherapy using an attenuated live strain of Mycobacterium bovis, is used as induction and maintenance intravesical therapy for patients with intermediate- and high-risk NMIBC.
- D. Chemotherapy agents, including Mitomycin C, Doxorubicin, and Epirubicin, may be given as induction intravesical chemotherapy for intermediate- or high-risk NMIBC patients.
- E. Gemcitabine, Docetaxel, Paclitaxel, and Valrubicin are intravesical options for patients who are unfit or unwilling to undergo cystectomy and/ or demonstrate BCG-refractory disease.

VII. Patient Assessment:

- A. Physical Exam:
 - 1. Patient identification (Name and DOB), medication allergies (to include Betadine and latex), reactions to prior courses of intravesical therapy, and current medications must be reviewed prior to treatment.
 - 2. Confirmation of written or electronic physician order and treatment series number, if indicated. Utilize the 5 "rights" of medication administration safety:
 - i. Right patient
 - ii. Right route
 - iii. Right time
 - iv. Right dose
 - v. Right medication
 - 3. Assessment of vital signs to include BP, pulse, and temperature to be taken before the procedure, if indicated.
 - 4. Assessment of constitutional symptoms of general well-being:
 - i. If a patient feels unwell with dysuria or other irritative bladder symptoms, has had a recent fever, or has had gross hematuria that day, instillation should be deferred.
 - a. Send urine for culture, and discuss the findings with the prescribing clinician.
 - b. Consider sending the patient home on an antibiotic pending the culture results.
 - c. Asymptomatic microscopic hematuria or isolated white blood cells should not preclude treatment with BCG.
 - 5. Assessment of ability to retain solution for the desired dwell time:

- i. Anticholinergics may be prescribed if the patient complains of bladder spasms.
 6. Empty the bladder prior to instillation of medication for maximum medication concentration in bladder.
- B. Documentation:
 1. All the above.
 2. Also, document the lot number, expiration date and post procedure instructions and teaching (both verbal and written). In addition, document the names of the personnel checking the chemotherapeutic agent during a time out. Document dwell time if indicated.

VIII. Contraindications to Administration:

Patients who are pregnant or lactating, have liver disease, a history of active or prior tuberculosis should not receive chemotherapeutic drugs. (Uyen, 2014)

- A. Intravesical BCG is contraindicated (but not limited to) the following conditions:
 1. Within 7 to 14 days of bladder or prostatic surgery, including biopsy
 2. Within 7 to 14 days following traumatic catheterization
 3. Traumatic catheterization or gross hematuria day of treatment
 4. Immunosuppressed patients with congenital or acquired immune deficiency, whether due to concurrent disease (e.g., AIDs, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation) or immunosuppressive therapy (e.g., corticosteroids, DMARDs).
 - a. If these conditions are present, but treatment is still deemed necessary, informed consent should be discussed by prescribing provider and documented in patient's record. (Herr, 2013)
 5. Symptomatic urinary tract infection
 6. In the presence of febrile illness
 7. Patients on treatment with certain antibiotics that may interfere with effectiveness of BCG.
 - a. Discuss with prescribing or collaborating provider before administration.
 - b. Fluoroquinolones should be used with caution as they may alter the therapeutic effects of BCG.
 8. Any previous allergies or adverse reactions to BCG.
- B. Intravesical chemotherapy is contraindicated (but not limited to) the following conditions:
 1. Any previous allergy or adverse reactions to the chemotherapeutic agent
 2. Bladder perforation

IX. Universal Protocol (UP):

- A. Universal hand washing practices are an important intervention in the prevention of contamination with hazardous drug/materials and infectious waste. (Washburn, 2007) This includes proper hand washing before and after any contact with the drug

or agent, patient's waste, plastic back absorptive drapes/liners and equipment. Repeat thorough hand washing after the clean-up. Hand washing should occur before and after any glove use.

- B. Sterile technique is required for urethral catheterization.
- C. Biohazardous or chemotherapy waste container
- D. Spill kit
- E. Eyewash station
- F. Personnel protective equipment: chemotherapy gloves (non-powdered, polyvinylchloride or nitrile gloves) or double gloves; disposable, non-permeable gown; surgical mask or face shield; protective eye gear. An N-95 respirator may be used if preferred by local institution policy.
- G. Safe Work Practices – Adherence to recommended work practices and use of engineering controls (i.e., use of biological safety cabinets or closed systems) and PPE has been shown to substantially reduce worker exposure to hazardous drugs. (Connor, 2006) Factors that can adversely affect how safely these drugs are handled include increased workload, understaffing, improper training, budgetary constraints, and use of more complex treatment regimens. (NIOSH 2004 Alert)

X. Preparation of Agent:

- A. BCG:
 1. The dose for the intravesical treatment of BCG is one vial suspended in 50 mL preservative free saline (0.9% Sodium Chloride Injection U.S.P).
 2. BCG **must be used** within 2 hours of reconstitution. Unused solution is discarded as biohazardous waste after 2 hours.
 3. The preparation of BCG suspension must be done using aseptic technique. To avoid cross contamination, parental drugs are not prepared in areas where BCG has been prepared.
 4. All equipment, supplies, and receptacles in contact with BCG are handled and disposed of as biohazards.
 5. The individual responsible for mixing the agent should wear chemotherapy gloves or double gloves and take precautions to avoid contact of BCG to broken skin. If preparation cannot be performed in a biocontainment hood, then a mask, face shield, and non-permeable gown should be worn to avoid inhalation and inadvertent exposure to broken skin. (TICE product insert)
 6. Do not use a filter with BCG instillation.
 7. Can be reconstituted via syringe method or using closed system administration supplies. See package insert.
 8. Avoid exposing BCG to direct sunlight.
 9. In case of BCG shortage:
 - i. The global shortages in TICE BCG that occurred in 2014 and 2019 led the AUA to recommend several management strategies to maintain high quality care for patients. These recommendations may

supersede statements described herein related to BCG administration.

- ii. The AUA Statement on the BCG Shortage is available at <https://www.auanet.org/about-us/bcg-shortage-info>.

B. Mitomycin:

1. The dose for Mitomycin is 40 mg reconstituted in 20 mL sterile water. Should take place in a biological safety cabinet Class II, Type A or in a closed system drug transfer device.
2. The preparation of Mitomycin should be done using aseptic technique. The individual responsible for mixing the agent should wear chemotherapy gloves/double gloves and take precautions to avoid contact to skin as Mitomycin is a vesicant. If preparation cannot be performed in a biocontainment hood, then a mask and double gloves should be worn and mixed in a closed system drug transfer device.
3. All equipment, supplies and receptacles in contact with cytotoxic agents are handled and disposed of as chemotherapy waste.

C. Gemcitabine:

1. Follow institutional policies for preparation of hazardous medications when preparing Gemcitabine.
2. Use Gemcitabine powder for injection 1 g or 2 g vials.
3. Reconstitute Gemcitabine 1000 mg/ 50 mL normal saline or 2000 mg/ 50-100 mL normal saline, or use premixed gemcitabine with closed system administration set. (Addeo, 2010; Cockerill, 2015; Dalbagni, 2006; Di Lorenzo, 2010; Skinner, 2013)
4. Containers should be clearly marked “For irrigation only” to avoid accidental intravenous administration.
5. All equipment, supplies, and receptacles in contact with cytotoxic agents are handled and disposed of as chemotherapy waste.

D. Docetaxel:

1. Follow institutional policies for preparation of hazardous medications when preparing Docetaxel.
2. Reconstitute Docetaxel 75 mg/ mL normal saline. (Barlow, 2009)
3. Containers should be clearly marked “For irrigation only” to avoid accidental intravenous administration.
4. All equipment, supplies, and receptacles in contact with cytotoxic agents are handled and disposed of as chemotherapy waste.

XI. Administrative Precautions:

- A. BCG: Utilize a separate biohazard bag for all disposable equipment and drug disposal in procedure room for immediate disposal.
- B. Mitomycin, Gemcitabine, and Docetaxel: Place all equipment and waste in a separate puncture-resistant yellow chemotherapy waste container with a chemotherapy trash can liner.

- C. Know where the chemotherapy spill kit is located in your area. Manage spills according to established, written policies and procedures for the workspace. Commercial chemotherapy spill kits are available. Only designated, trained staff members should clean up chemotherapy spills. (Mellinger, 2010)
- D. Know the location of the eyewash station, if available. For an eye exposure with a chemotherapeutic agent, the affected eye(s) should be flushed immediately with water or an isotonic eye wash for 15 minutes and medical attention sought immediately. (Mellinger, 2010)
- E. Consider closed-system products with needleless systems when transferring from primary packaging to instillation equipment. Follow aseptic procedure and local guidelines for safe handling of hazardous drugs.
- F. Never remove tubing from IV bags or containers with a hazardous drug.
- G. Wash hands with soap and water before donning protective gloves.
- H. Utilize proper PPE to include chemotherapy gloves or at a minimum, double glove; a disposable, non-permeable gown; surgical mask or face shield; goggles (optional). An N-95 respirator may be utilized if preferred by local institution policy.
- I. Sterile catheter kit and 14 Fr Foley or straight catheter for females and 14 Fr coudé or straight catheter for men.
- J. Place plastic back absorptive liners under the patient to protect the perineal area during catheter insertion and removal. Have a gauze pad to help absorb any drops during the administration of agent into catheter. In addition, have a washcloth with soapy water ready to cleanse the perineum and any skin on the patient exposed to agent.
- K. Disposable sheet for patient privacy and protection.
- L. Lidocaine Jelly (2%) may be used. Some urologists prefer it not be used with BCG, Mitomycin, Gemcitabine, or Docetaxel. Follow facilities guidelines regarding use.

XII. Goals of Procedural Intervention:

Treatment of NMIBC. Intravesical therapy has a well-established role in the treatment of non-muscle invasive bladder cancer. See [Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Joint Guideline \(2020\)](#).

XIII. Procedure:

- A. Answer any questions or concerns about treatment and reinforce instructions to ensure compliance and minimize complications.
 - 1. Perform sterile catheterization with 14 Fr straight or 14F coudé (male) catheter per clinic/unit protocol. Empty bladder completely.
 - 2. Insert a catheter tip syringe containing the treatment with an adaptor at the tip of the syringe to prevent spillage or splash during insertion. Or, insert the primed tubing attached to medication vial into catheter.
 - i. Instill BCG, Mitomycin, or Gemcitabine per gravity flow or by gentle push instillation.

- ii. Administer Docetaxel irrigation into the bladder by slow push or gravity flow through a catheter over a 5-minute period. (Barlow, 2009)
3. Assess the patient for pain.
4. Remove the syringe or medication vial with tubing intact. Squeeze the catheter closed and remove the catheter or plug the catheter as indicated, using sterile gauze to help absorb any drops. If the patient has trouble holding the solution, a Foley catheter may be used, and a catheter plug may be inserted onto the end of the catheter after instillation so that the chemotherapeutic agent remains in the bladder for a specified amount of time, usually one to two hours. Depending on the patient's mobility, the catheter may be removed at the end of the desired dwell time, or the patient may be connected to a urinary drainage bag to drain the chemotherapeutic agent.
5. Once the catheter is removed, discard appropriately, repeat inspection of the perineal area for leaks, and reassess for pain. Cleanse the area as indicated.
6. Instruct the patient to attempt to retain the treatment for 1 to 2 hours. Historically, the patient has been instructed to lie down and reposition every 15 minutes from left side to right side, then on back to dislodge air bubbles from the catheter and to ensure that the medication comes in contact with all of the areas of the bladder. However, there is no evidence to support this practice.
7. Reinforce patient post procedure instructions and schedule an appropriate follow up visit.

XIV. Side Effects:

Potential Side Effects and Complications of Bladder Cancer Intravesical Treatment (Table 1):

BCG	Docetaxel	Gemcitabine	Mitomycin C
BCG sepsis	Dysuria	Anemia	Dermatitis
Bladder contracture	Dermatitis	Asthenia	Anorexia
Bladder ulceration	Facial flushing	Bladder spasms	Bladder contracture
Cough	Hematuria	BUN elevation	Bladder pain
Cystitis	Urinary frequency	Cellulitis	Cystitis
Epididymo-orchitis	Urinary tract infection	Chills	Diarrhea
Fever	Urinary urgency	Cystitis	Dysuria
Flank pain		Dermatitis	Fatigue
Granulomatous hepatitis		Dysuria	Hematuria
Hematuria		Fatigue	Nausea
Lymphadenitis		Genitourinary infection	Palmer desquamation
Lymphadenopathy		Genitourinary perforation	Suprapubic pain

Mycotic aneurysms		Headache	Vomiting
Nephritis		Heavy legs	
Nocturia		Hematuria	
Orchialgia		Hot flashes	
Penile lesions		Infection/ pulmonary	
Prostatitis		Leukopenia	
Pulmonary tuberculosis		LFT elevation	
Pyelonephritis		Nausea	
Reactive arthritis		Pain (not urologic or gastrointestinal)	
Spondylitis		Sexual pain	
Testicular swelling		Suprapubic pain	
Ureteral obstruction		Sweating	
Urinary frequency		Thrombocytopenia	
Urinary incontinence		Urinary frequency	
Urinary urgency		Urinary incontinence	
		Urinary tract infection	
		Urinary urgency	
		Voiding dysfunction	
		Vomiting	

XV. Patient Education:

Restrict fluid intake, consumption of caffeinated beverages and use of diuretics 4 hours prior to procedure, if possible.

A. BCG:

1. Patient instruction: Do not void for 1 to 2 hours post procedure, if possible.
2. Precautions post procedure: after the first void and for the next 6 hours:
 - a. Sit to void to avoid urine splashing. Do not use public toilets or void outside.
 - b. After each void add 2 cups undiluted bleach to toilet, close the lid and wait 15-20 minutes and then flush the toilet. Repeat with each void for 6 hours.
 - c. Increase fluid intake to dilute the urine. Begin after the first void post procedure.
 - d. Common side effects within 24 hours post procedure include blood in the urine; low grade fever (99-100° F); tiredness; urinary frequency, urgency, and burning with urination; and muscle or joint achiness. You will be given prescriptions to address the urinary symptoms (frequency, urgency, and burning on urination) if needed.

- e. If sexually active, wear a condom with intercourse throughout the entire treatment course.
 - f. Urinary incontinence: immediately wash clothes in clothes washer. Do not wash with other clothes.
 - g. If wearing an incontinence pad, pour bleach on pad, allow to soak in, then place in plastic bag and discard in trash.
 - h. Call the urology clinic or provider if you develop a fever over 101.3° F (38.5°C), chills or rigors.
 - i. May use acetaminophen or ibuprofen for fever and body aches.
 - j. May need antispasmodic medication to help with frequency and urgency.
- B. Mitomycin or other chemotherapy agents:
- 1. If recommended by the clinician, take oral sodium bicarbonate 1.3 gm, the night before, morning of, and 30 minutes prior to treatment. This may help improve effectiveness of medication to decrease recurrences of bladder tumors.
 - 2. Patient instruction: Limit fluid intake the day before and day of treatment.
 - 3. Do not void for 1 to 2 hours post procedure, if possible.
 - 4. Sit to void to avoid urine splashing. Do not void outside.
 - 5. Flush the toilet twice after the first void.
 - 6. Wash the perineum or glans after voiding to decrease irritation from chemical.

References

1. Addeo R, Caraglia M, Bellini S et al. Randomized phase III trial on gemcitabine versus mitomycin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. *J Clin Oncol* 2010; **28**: 543.
2. Approach to Address Limited Supply of TICE® Bacillus Calmette-Guerin (BCG). Available at <https://www.auanet.org/practice-resources/bcg-info/bcg-shortage-notice>.
3. Au, JL, Badalament, RA, Wientjes, MG, et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J Natl Cancer Inst* 2001; **93**: 597.
4. Barlow L, McKiernan J, Sawczuk I, Benson M. A single-institution experience with induction and maintenance intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to bacille Calmette-Guérin therapy. *BJU Int*. 2009 Oct; **104**: 1098.
5. Barlow LJ, McKiernan JM and Benson MC. The novel use of intravesical docetaxel for the treatment of non-muscle invasive bladder cancer refractory to BCG therapy: a single institution experience. *World J Urol* 2009; **27**: 331.
6. CDC - NIOSH Publications and Products - Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings. Available at <https://www.cdc.gov/niosh/docs/2004-165/default.html>.
7. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. *J Urol* 2016; **196**: 1021.

8. Cockerill PA, Knoedler JJ, Frank I et al. Intravesical gemcitabine in combination with mitomycin C as salvage treatment in recurrent non-muscle-invasive bladder cancer. *BJU Int* 2015; **117**: 456.
9. Connor, TH, McDiarmid, MA. Preventing occupational exposures to antineoplastic drugs in health care settings. *CA Cancer J Clin* 2006; **56**: 354.
10. Dalbagni G, Russo P, Bochner B et al. Phase II trial of intravesical gemcitabine in bacille Calmette-Guérin-refractory transitional cell carcinoma of the bladder. *J Clin Oncol* 2006; **24**: 2729.
11. Di Lorenzo G, Perdoni S, Damiano R et al. Gemcitabine versus Calmette-Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. *Cancer* 2010; **116**: 1893.
12. Griffin, JG, Holzbeierlein, JM. Side effects of perioperative intravesical treatment and treatment strategies for these side effects. *Urol Clin North Am* 2013; **40**: 197.
13. Herr, HW, Dalbagni, G. Intravesical bacille Calmette-Guérin (BCG) in immunologically compromised patients with bladder cancer. *BJU Int* 2013; **111**: 984.
14. Liu Y, Lu J, Huang Y, Ma L. Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guérin for Bladder Cancer. *J Oncol*. 2019 Mar 10; **2019**: 6230409.
15. Maffezzini, M, Campodonico, F, Manuputty, EE, et al. Systemic absorption and pharmacokinetics of single-dose early intravesical mitomycin C after transurethral resection of non-muscle-invasive bladder cancer. *Urology* 2013; **82**: 400.
16. McKiernan JM, Masson P, Murphy AM, et al. Phase I trial of intravesical docetaxel in the management of superficial bladder cancer refractory to standard intravesical therapy. *J Clin Oncol*. 2006 Jul 1; **24**: 3075.
17. Mellinger E, Skinner L, Sears D, et al. Safe handling of chemotherapy in the perioperative setting. *AORN J* 2010; **91**: 435.
18. Messing EM, Tangen CM, Lerner SP, et al. Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non-Muscle-Invasive Bladder Cancer on Tumor Recurrence: SWOG S0337 Randomized Clinical Trial. *JAMA*. 2018 May 8; **319**: 1880.
19. Messing, EM, Tangen, CM, Lerner, SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. *JAMA* 2018; **319**: 1880.
20. Montoya, L. Managing hematologic toxicities in the oncology patient. *J Infus Nurs* 2007; **30**: 168.
21. Polovich, M, Martin, S. Nurses' use of hazardous drug-handling precautions and awareness of national safety guidelines. *Oncol Nurs Forum* 2011; **38**: 718.
22. 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.
23. To, U, Kim, J, Chia, D. Disseminated BCG: complications of intravesical bladder cancer treatment. *Case Rep Med* 2014; 1.

24. Waddell, J, Moussavian, P, Solimando, D. Intravesical Gemcitabine for Superficial Bladder Carcinoma. Hospital Pharmacy 2004; **39**: 1153.
25. Washburn, DJ. Intravesical antineoplastic therapy following transurethral resection of bladder tumors: nursing implications from the operating room to discharge. Clin J Oncol Nurs 2007; **11**: 553.
26. Zhao, LC, Meeks, JJ, Helfand, BT, et al. Screening urine analysis before bacille Calmette-Guérin instillation does not reduce the rate of infectious complications. BJU Int 2011; **109**: 1819.