



## INTRAVESICAL ADMINISTRATION OF THERAPEUTIC MEDICATION STANDARD OPERATING PROCEDURE

Approved by the AUA Board of Directors July 2015

### I. STATEMENT OF PURPOSE:

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

### 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 bladder via catheterization utilizing sterile technique for interstitial cystitis flares, or non-muscle invasive bladder cancer 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 and interstitial cystitis. 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. Non-muscle invasive urothelial carcinoma of the bladder

1. Intravesical Bacillus Calmette-Guerin (BCG) is an immunotherapy using an attenuated live strain of *Mycobacterium bovis* used as a therapy for and prophylaxis against, recurrent tumors in patients with intermediate and high risk non-muscle invasive urothelial bladder cancer (recurrent or high volume low grade Ta tumors; carcinoma in situ; or high grade Ta or T1 tumors).

2. Interferon Alpha (Intron-A) may be combined with BCG and this combination may be effective in patients with tumor recurrence after BCG alone.
  3. Intravesical Mitomycin is a cytotoxic antibiotic that inhibits DNA synthesis in bladder cancer cells. It may be given immediately, post-transurethral resection of bladder tumor (TURBT) in absence of perforation. Sodium bicarbonate, which raises the pH of serum and urine, may be used orally in combination with Mitomycin to buffer urine pH to optimize therapy and decrease recurrence of bladder tumors (Au, 2001).
  4. Valrubicin (Valstar) is used for BCG refractory carcinoma in situ. It is a cytotoxic agent.
  5. Epirubicin, Gemcitabine, Thiotepa, Doxorubicin, and Adriamycin are examples of other cytotoxic agents that may be used as second line therapies for bladder cancer.
  6. Data for intravesical therapy for pure non-urothelial bladder cancer histologies (adenocarcinoma, pure squamous cell carcinoma, small cell or neuroendocrine tumors) is lacking and should not be offered.
- B. Interstitial cystitis
1. In interstitial cystitis, a cocktail or combination of medications may be used including varying combinations of the following medications based on prescriber's protocol.
  2. DMSO, RIMSO-50 (dimethyl sulfoxide intravesical) is a medication that exerts anti-inflammatory, antioxidant and analgesic in the bladder. Only used in patients with interstitial cystitis. It is NOT indicated in bladder cancer.
  3. Lidocaine or Marcaine are analgesic agents that stabilize neuronal cell membranes and inhibit nerve impulse initiation and conduction. Either of these agents may be used in cocktails for interstitial cystitis.
  4. Sodium bicarbonate- raises pH of serum and urine. Used in interstitial cystitis cocktails to neutralize the pH and decrease bladder irritation from other medications in cocktail.
  5. Heparin-used in intravesical cocktails for interstitial cystitis. Believed to help reestablish the GAG layer of bladder. Does not cause alteration in INR when given intravesically.
  6. Triamcinolone, Solucortef or Solumedrol are steroid anti-inflammatory medications used in interstitial cystitis.

## **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: right patient, right route, right time, right dose, and right medication
3. Assessment of vital signs to include: BP, pulse, and temperature to be taken before the procedure
4. Assessment of constitutional symptoms of general well-being
5. Assessment of ability to retain solution for the desired dwell time. Anticholinergics may be prescribed if patient complains of bladder spasms.
6. Perform a urine analysis (UA) prior to instillation. If bacteriuria is present on HPF or if > 5 WBCs is present on HPF and/or gross hematuria is noted and the patient is symptomatic,

defer instillation and send for urine culture to include identification and sensitivity of all organisms. Discuss findings with prescribing clinician. Consider sending patient home on an antibiotic. Microscopic hematuria only or isolated WBCs in an otherwise asymptomatic patient should not preclude treatment.

7. Perform a perineal inspection and pain assessment (bladder, back or pelvic) before, during and after the instillation.
  8. Completely drain 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 or are immunosuppressed 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. Pregnant or lactating patients
  5. Active tuberculosis
  6. Immunosuppressed patients with congenital or acquired immune deficiency, whether due to concurrent disease (e.g. AIDs, leukemia, lymphoma), cancer therapy (cytotoxic drugs, radiation) or immunosuppressive therapy (e.g. corticosteroids, DMARDs). If these conditions are present, but treatment is still deemed necessary, informed consent must be discussed by prescribing provider and documented in patient's record. (Herr, 2013).
  7. Symptomatic urinary tract infection
  8. In the presence of febrile illness
  9. Patients on treatment with certain antibiotics that may interfere with effectiveness of BCG. Discuss with prescribing or collaborating provider before administration. Flouroquinolones should be used with caution as they may alter the therapeutic effects of BCG.
  10. Any previous allergies or adverse reactions to BCG.
- B. Intravesical Mitomycin is contraindicated (but not limited to) the following conditions:
1. Any previous allergy or adverse reactions to Mitomycin
  2. Bladder perforation
  3. No monitoring of INR, CBC or hepatic function is necessary as very low systemic absorption occurs when instilled intravesically (Maffezzini, 2001).
  4. Pregnant or lactating women

### **IX. UNIVERSAL PROTOCOL (UP):**

- A. Universal hand washing practices is 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 nitrate 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 bio hazardous 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 bio hazardous.
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 reconstitution supplies provided with BCG. See package insert.
8. Avoid exposing BCG to direct sunlight.

##### B. Mitomycin:

1. The dose for Mitomycin is 40mg 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. Alkalinization of urine with oral 1.3 gm sodium bicarbonate the night before, morning of and 30 minutes prior to treatment or combination of sodium bicarbonate solution with Mitomycin for intravesical instillation may help improve effectiveness of medication to decrease recurrences of bladder tumors.
  4. All equipment, supplies and receptacles in contact with cytotoxic agents are handled and disposed of as Chemotherapy waste.
- C. Interstitial cystitis medication cocktail:
1. See AUA Guideline 2014 *Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome* (<http://www.auanet.org/education/guidelines/ic-bladder-pain-syndrome.cfm>) for treatment options and algorithm.
  2. There are various combination cocktails for intravesical instillation including DMSO alone or in combination with sodium bicarbonate, heparin and steroid. Some cocktails do not use DMSO at all.
  3. None of the medications for interstitial cystitis are bio hazardous or cytotoxic so may be mixed and disposed of in sharps container and regular trash.

## **XI. ADMINISTRATIVE PRECAUTIONS:**

- A. BCG: Utilize a separate biohazard bag for all disposable equipment and drug disposal in procedure room for immediate disposal. Mitomycin: Place all equipment and waste in a separate puncture-resistant yellow chemotherapy waste container with a chemotherapy trash can liner.
- B. Know where 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).
- C. Know location of 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).
- D. 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.
- E. Never remove tubing from IV bag or container with a hazardous drug.
- F. Wash hands with soap and water before donning protective gloves.
- G. 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.
- H. Sterile catheter kit and 14 Fr Foley or straight catheter for females and 14 Fr coude' or straight catheter for men.
- I. 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.

- J. Disposable sheet for patient privacy and protection.
- K. Lidocaine Jelly (2%) Urojet may be used. Some urologists prefer it not be used with BCG or Mitomycin, follow facilities guidelines regarding use.

## **XII. GOALS OF PROCEDURAL INTERVENTION**

- A. Treatment of non-muscle invasive bladder cancer. Intravesical therapy has a well-established role in the treatment of non-muscle invasive bladder cancer. See AUA Guidelines for the *Management of Non-Muscle Invasive Bladder Cancer (States Ta, T1 and Tis: Update (2007))*. <http://www.auanet.org/education/guidelines/bladder-cancer.cfm>
- B. Improvement in cystitis symptoms. See AUA Guidelines for *Interstitial Cystitis/Bladder Pain Syndrome*. <http://www.auanet.org/education/guidelines/ic-bladder-pain-syndrome.cfm>

## **XIII. PROCEDURE:**

- A. Bladder Cancer Treatment: 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 coude' (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 and instill agent per gravity flow or by gentle injection. Assess patient for pain.
  - 3. Remove syringe or medication vial with tubing intact. Squeeze catheter closed and remove catheter or plug 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 chemotherapeutic agent remains in the bladder for a specified amount of time, usually one to two hours. Depending on patient's mobility, the catheter may be removed at the end of the desired dwell time or patient may be connected to a urinary drainage bag to drain chemotherapeutic agent.
  - 4. Once catheter removed, discard appropriately, repeat inspection of perineal area for leaks and reassess for pain. Cleanse area as indicated.
  - 5. Instruct 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 catheter and to insure medication comes in contact with all areas of the bladder. However, there is no evidence to support this practice.
  - 6. Reinforce patient post procedure instructions and schedule an appropriate follow up visit.
- B. Interstitial Cystitis Treatment: Answer any questions or concerns about treatment and reinforce instructions to ensure compliance and minimize complications
  - 1. Perform sterile catheterization with 14 Fr straight catheter per unit or clinic protocol. Empty bladder completely.

2. Attach syringe to end of catheter and gently instill medication into bladder over 2 minutes or as tolerated by patient. Note time of instillation if indicated.
3. Remove catheter gently and discard appropriately.
4. Retain medication for desired time. Usually 1-2 hours. If the patient has a history of leaking post bladder instillation (BI), instruct patient to lay supine for up to 1 hour.
5. Instruct patient to follow plan for repeat treatments
  - a) Six weekly treatments or as tolerated with scheduled provider follow up
  - b) If improvement by fourth instillation but patient desires further improvement, consider 2 more weekly BIs for total of 6. Tailor plan to patient's needs.

C. Potential Side Effects and Complications of Bladder Cancer Intravesical Treatment:

Table 1

| Side Effects                 | Complications                      |
|------------------------------|------------------------------------|
| Dysuria                      | Urinary Tract Infection            |
| Urgency                      | Epididymitis/Orchitis              |
| Frequency                    | Abscess formation                  |
| Malaise                      | Hematuria with clot retention      |
| Arthralgia/Flu-like symptoms | Fever >101.3 degrees F (38.5°C)    |
| Low-grade Fever/chills       | Myelosuppression                   |
| Skin Rash/eruptions          | Ureteral obstruction               |
| Anorexia                     | Bladder contracture/necrosis       |
| Nausea/Vomiting              | BCG Sepsis                         |
| Urinary Incontinence         | Neutropenia                        |
| Bladder Spasms               | Tissue necrosis with extravasation |
| Hematuria                    | Pneumonitis                        |
|                              | Hepatitis                          |
|                              | Death                              |

1. Most antineoplastic drugs are non-selective in their mechanism of action and therefore, administration these agents into the bladder can induce an array of irritative voiding symptoms to include dysuria, frequency, urgency, suprapubic discomfort, hematuria and pelvic pain (Griffin, 2013). These symptoms are considered minor and are usually self-limiting requiring no further treatment. However, major side effects including sepsis, and pneumonitis can occur in <5% of patients (Uyen, 2014). Patients should be counseled on local and systemic reactions.
2. In the perioperative and clinic setting, extravasation of drug is a rare but serious complication that can result in peritoneal tissue necrosis, fistula formation, skin rash and severe, continuous pelvic pain (Washburn, 2007). Assessment of pain, using a validated pain scale, before, during and after the procedure is imperative. Releasing the agent and accumulated urine as soon as symptoms appear helps limit extravasation (Washburn, 2007). Cleansing the exposed skin area immediately after treatment is also important to limit exposure time.
3. Bone marrow suppression is more commonly associated with systemic intravenous (IV) therapies which directly enter the bloodstream (Montoya, 2007). A major advantage of

using intravesical therapy agents is minimal absorption due to administering the drugs locally in the bladder with decreased systemic side effects. Absorption of intravesical chemotherapy agents is dependent on molecular weight, concentration, and lipophilic properties as well as surgical technique (Griffin, 2013). The molecular weight of a drug has an effect on how easily it permeates cell membranes (Washburn, 2007). Thiotepa, an alkylating agent with a low molecular weight (189 Daltons) absorbs more easily into the blood stream and studies have shown systemic absorption when administered in the bladder (Griffin, 2013). Therefore, monitoring labs before and with subsequent treatments with Thiotepa is important.

D. Potential Side Effects of Interstitial Cystitis Intravesical Treatment:

Table 2

| Side Effects            |
|-------------------------|
| Dysuria                 |
| Urgency                 |
| Frequency               |
| Malaise                 |
| Urinary Incontinence    |
| Bladder Spasms          |
| Hematuria               |
| Urinary Tract Infection |

**XIV. PATIENT EDUCATION:**

Restrict fluid intake, 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 include:
  - 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: blood in urine; low grade fever (99-100 degrees 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 incontinence pad, pour bleach on pad, allow to soak in, then place in plastic bag and discard in trash.
  - h. Call urology clinic or provider if develops 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. Patient instruction: Do not void for 1 to 2 hours post procedure, if possible.
  2. Sit to void to avoid urine splashing. Do not void outside.
  3. Flush toilet twice after the first void.
  4. Wash perineum or glans after voiding to decrease irritation from chemical.
- C. Interstitial cystitis treatments:
  1. Instruct to hold treatment for up to 1 to 2 hours then void. No special precautions are necessary.

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