



TIPS AND TRICKS FOR BETTER TOLERABILITY OF INTRAVESICAL GEMCITABINE/DOCETAXEL THERAPY

Version 1.2, Feb 16, 2024

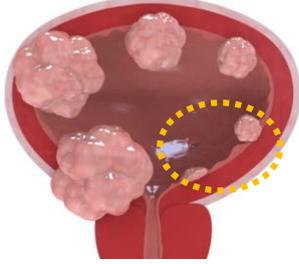


MICHAEL A. O'DONNELL, MOHAMAD ABOU CHAKRA

UNIVERSITY OF IOWA HOSPITALS AND CLINICS

IA, US

Intravesical Gem/Doce: Toxicity and Treatment



Non-Muscle Invasive Bladder Cancer (NMIBC)



A. Pre-Treatment Recommendations

The night before therapy

- Give **two 650 mg tablets** (total **1300 mg**) of oral sodium bicarbonate. *RECOMMENDED (except if sodium restricted)*. This alkalinizes the urine and helps avert the stinging effect of the gemcitabine (1 gram in 50 cc saline = pH 2.6) [1, 2].
- Make sure patients abstain from alcohol, caffeine, and diuretics for **four hours before** treatment, and limit oral fluid intake. *RECOMMENDED*

Morning of therapy (1 hour before)

- Give another (except if sodium restricted) **two 650 mg tablets** (totaling 1300 mg) of oral sodium bicarbonate [2]. *RECOMMENDED*
- Pretreat with anticholinergics such as **oxybutynin (5mg)** or with β_3 adrenoceptor agonists such as **Mirabegron (25 mg)**. *OPTIONAL (for those with history of frequency, urgency and/or spasms)*
- Give a benzodiazepine (**Diazepam 5-10 mg**) and an oral narcotic (**two tablets of oxycodone/acetaminophen 2.5 mg/325 mg**). *OPTIONAL (for those in whom anticholinergics or β_3 adrenoceptor agonists were insufficient)*
- Pretreat with **Naproxen 220-250 mg/ Ibuprofen 600mg** tablets as there is emerging evidence that NSAIDs can improve irritative bladder symptoms [3]. *RECOMMENDED (except when contra-indicated)*

Just before therapy

For patients that immediately have pain or spasm with instillation

- Pretreat with alkalinized lidocaine (**40 cc of 2% lidocaine** mixed with 4 cc standard sodium bicarbonate 8.4% liquid) X **10-15 min prior** to the first drug instillation. Drain immediately prior to drug instillation; do not rinse.
- This totally numbs the bladder and is ideally suited for patients with bladder pain.
- This works by preventing unmyelinated C fibers from conducting, thereby enhancing the bladder's functional storage capacity [4].



Absolute contraindications to anticholinergics

- Closed angle glaucoma
- A history of impaired gastric emptying or urinary retention.
- Caution advised in the elderly, especially those with cognitive impairment



- ⚡ If anticholinergics are contraindicated in elderly patients, there is some emerging data that Mirabegron will improve the irritative symptoms caused by BCG [5] *NOTE: Blood pressure monitoring is advised after administration of mirabegron.*
- ⚡ Elderly persons are typically advised to take short-half-life benzodiazepines, such as triazolam, alprazolam, and oxazepam, since they do not build up in the blood [6].

B. During Treatment Modifications

Using the proper materials for catheterisation

- Foley catheters of **14–16 FR** size are preferred.
- Coudé catheters** are typically better tolerated by older men.
- A hydrophilic catheter** may be used; if not available, at least 5–10 ml of lubricant or lidocaine jelly is recommended.
- Foley balloons are inflated to a **maximum of 5–10 cc**.
- The patient is instructed to stay supine with occasional rolling side to side every 10–15 minutes.
- 60-minute exposure** per drug is sufficient.
- The use of a closed system from instillation of drugs to disposal is crucial to minimizing the exposure risk of staff and patients to neoplastic drugs **[See appendix on page 4]**.

Split dosing method

- Split dosing with **half of the drug, half of the time interval**, but repeated X2 **[7]**.
- This makes for a total of **four instillations** with an identical total dwell time for each drug but at reduced bladder volume.
- Example: 25 cc of gemcitabine for 45 min; drain, then repeat. Then administer 25 cc of docetaxel for 45 minutes, then repeat.
- Recommended for patients with a clearly diminished bladder capacity.**

Gravity/reflux method

- After administering the first drug, connect the foley to a new drainage bag raised two to three feet on an IV pole so that gravity draws the medication into the bladder instead of plugging or clamping **[See appendix on page 4]**.
- The tubing serves as a reservoir that permits reflux of the drug during spasms**; however, the medication returns to the bladder after the spasm passes **[7]**.
- In this manner, minimal to no medication is lost.
- Repeat the same technique with the docetaxel instillation.
- Recommended for patients who repeatedly spasm.**



- ✚ A proper timer should be set for the appropriate dwell time. Additional time during drug instillation may increase side effects.



- ✚ A proper history before each instillation session allows the clinician to decide which technique should be used to administer the drugs, i.e., when bladder spasm occurs frequently, the gravity/reflux technique is preferable.



- ✚ For patients who have had no difficulty holding the first medication, the catheter may be removed 5-10 minutes after the second drug is administered with instructions to void 60-90 minutes later.
- ✚ Patients who cannot hold the second medication should be kept in the clinic supine until the dwell time is completed and then drained by gravity.

C. Post Treatment Recommendations



- **Counsel patients** about anticipated side effects and appropriate treatment plans.
- Reminding patients of their next visit is crucial to ensuring compliance.
- Provide the patient with **an appointment card** that summarizes the doses administered.



- To alleviate occasional nausea, **4 mg of oral ondansetron** before patient discharge should be given and repeated **8 hours later** if necessary.
- Mild-to-moderate fatigue has been reported to **resolve in 24-48 hours** with rest.
- Fatigue typically doesn't affect the patient's capacity to carry out regular activities or their ability to perform physically.



- There is **no special precaution to clean toilets** after the drainage of the bladder; the use of appropriate disinfective wipes is recommended. All sites of skin contact should be gently washed with soap and water.
- When patients cannot leave their beds to enter the toilet, **urinals should be used carefully**, as the risk of drug spillage may increase.

Expected side effects of Gem/Doce

	Urinary frequency (%)	Urgency (%)	Dysuria (%)	Hematuria (%)	UTI (%)	Nausea (%)	Asthenia (%)	Rash (%)	Grade III AE (%)	Adverse events affecting treatment schedule
Weighted Mean Results [8]	22%	21.6%	14%	9.6%	8.8%	7.5%	6.4%	6%	1%	9.1%

Better tolerability ensures better efficacy

- ✚ At least **five of the six induction** doses should be given for adequate therapy.
- ✚ Maintenance therapy of monthly instillations for **24 months** is recommended if no recurrence occurs after completing induction.

Appendix

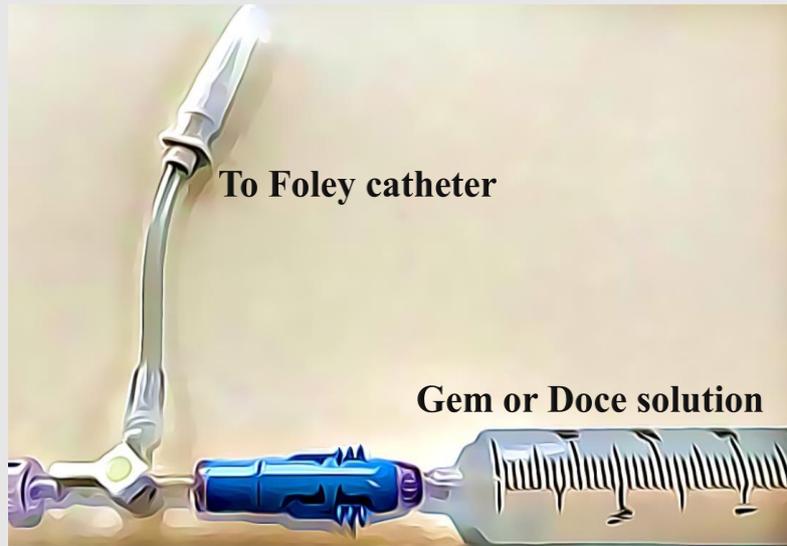
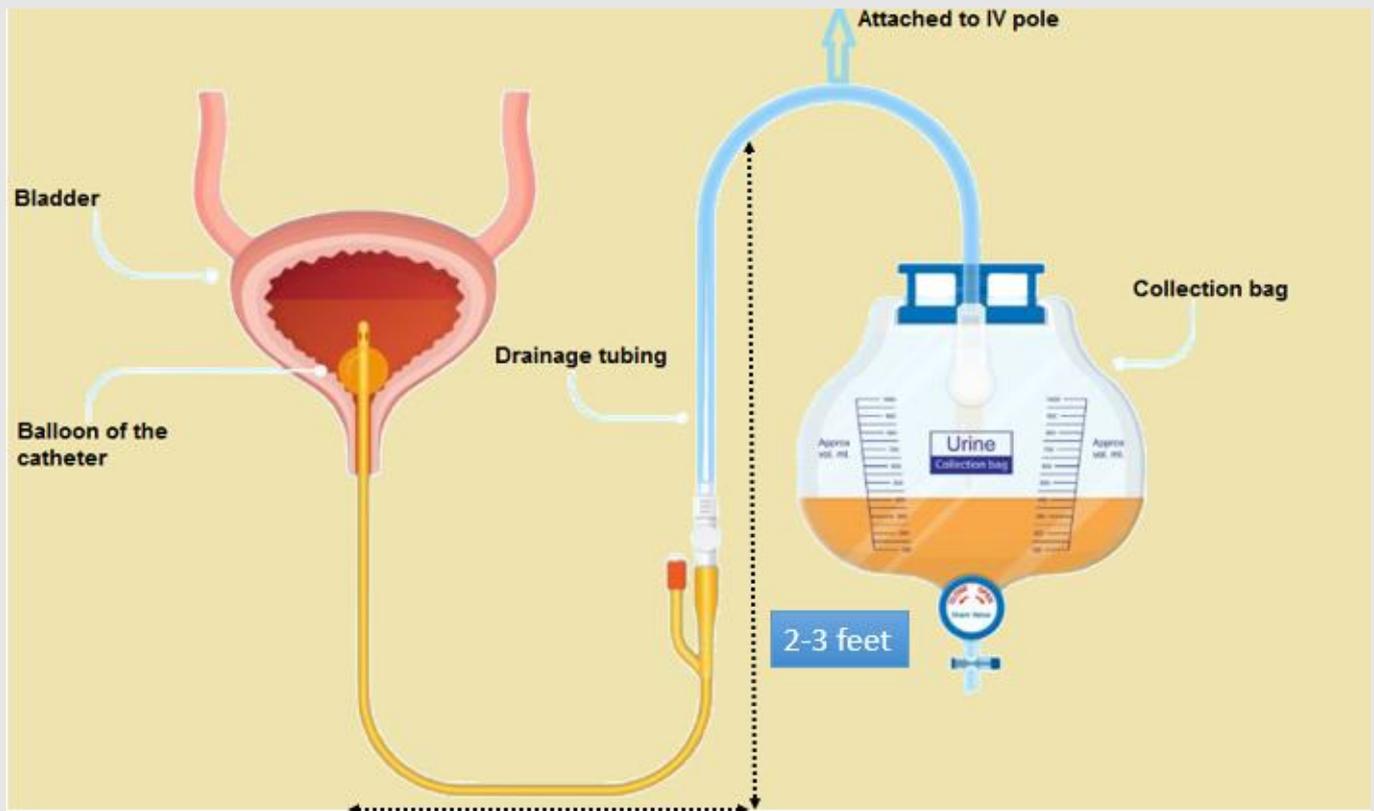


Figure 1 Intravesical Gem/Doce instillation through a closed system.



When a bladder spasm occurs, the medication that was previously ejected from the bladder flows into the tubing before returning to the bladder when the spasm stops

Figure 2 'Gravity/Reflux' technique

Supporting Medical Literature

- 1-Abou Chakra M, Packiam VT, O'Donnell MA. Real-world efficacy of adjuvant single-agent intravesical gemcitabine for non-muscle invasive bladder cancer. *Expert Opin Pharmacother*. 2023;1-11.
- 2-McElree IM, Steinberg RL, Mott SL, et al. Comparison of Sequential Intravesical Gemcitabine and Docetaxel vs Bacillus Calmette-Guérin for the Treatment of Patients With High-Risk Non-Muscle-Invasive Bladder Cancer. *JAMA Netw Open*. 2023 Feb 1;6(2):e230849.
- 3-Kahokehr A, Vather R, Nixon A, et al. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. *BJU Int*. 2013 Feb;111(2):304-11.
- 4- Evans RJ. Intravesical therapy for overactive bladder. *Curr Urol Rep*. 2005 Nov;6(6):429-33.
- 5-Sun K, Wang D, Wu G, et al. Mirabegron improves the irritative symptoms caused by BCG immunotherapy after transurethral resection of bladder tumors. *Cancer Med*. 2021 Nov;10(21):7534-7541.
- 6-Bogunovic OJ, Greenfield SF. Practical geriatrics: Use of benzodiazepines among elderly patients. *Psychiatr Serv*. 2004 Mar;55(3):233-5.
- 7- McElree IM, Mott SL, O'Donnell MA, et al. Alternative instillation techniques of sequential intravesical gemcitabine and docetaxel for non-muscle-invasive bladder cancer. *BJU International*. Published online October 26, 2023.
- 8- Abou Chakra M, Packiam VT, Duquesne I, et al. Combination intravesical chemotherapy for non-muscle invasive bladder cancer (NMIBC) as first-line or rescue therapy: where do we stand now? *Expert Opin Pharmacother*. 2024 Jan 24:1-12.