The Use of Botulinum Neurotoxin Type A in a Patient With Refractory Urge Incontinence to Facilitate the Intravesical Treatment of Bladder Carcinoma

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Intravesical Bacillus Calmette-Guérin (BCG) has become the preferred initial treatment after resection of high-grade T1 urothelial carcinoma and carcinoma in situ (CIS). We report the case of a patient with high-grade T1 urothelial carcinoma and CIS who was treated with intravesical BCG. Due to the patient's severe urge incontinence, however, the BCG solution leaked from the bladder immediately upon instillation. We describe our experience of using botulinum neurotoxin A intradetrusor injections to facilitate successful intravesical therapy by increasing bladder capacity to enable the BCG to remain in the patient's bladder for the appropriate treatment duration.

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KEY WORDS

Bacillus Calmette-Guérin • Bladder carcinoma • Botulinum neurotoxin • Gemcitabine • Urge incontinence

The role of intravesical Bacillus Calmette-Guérin (BCG) in treating residual papillary lesions, decreasing recurrence, and reducing the risk of progression has been shown in several studies.[1-3] After BCG therapy, the initial tumor-free response rate has been reported as high as 84%.[4] Approximately half of patients receiving BCG treatment achieve a long-term response for a median of 4 years. As such, BCG is the preferred first-line treatment for carcinoma in situ (CIS) by the American Urological Association Guidelines Panel.[5]

Botulinum toxin is a neurotoxin formed by the bacterium *Clostridium botulinum* that inhibits the release of acetylcholine at the neuromuscular junction to cause muscle paralysis.[6] Dykstra and Sidi[7] first described the use of botulinum neurotoxin

type A (BoNT/A) in the lower urinary tract with the treatment of detrusor-sphincter dyssynergia with injection into the urethral sphincter.[7] A decade later, Schurch and colleagues[8] used BoNT/A in the treatment of urinary incontinence in patients with spinal cord injuries. Since its US Food and Drug Administration approval, BoNT/A has become a second-line therapy for neurogenic detrusor overactivity with urinary incontinence and overactive bladder in patients who are refractory to or intolerant of antimuscarinic therapy. We describe the use of BoNT/A intradetrusor injections to facilitate the use of intravesical BCG in a patient with severe urge incontinence refractory to first-line therapy.

Case Report

A 74-year-old man presented with a 6-month history of urge incontinence. He reported complete loss of urine approximately three times daily and complete saturation of his diaper overnight. He had tried several antimuscarinic medications with dose escalation; however, he had persistent leakage. He had a history of hypertension, hyperlipidemia, and severe right hip osteoarthritis for which he required a wheelchair for mobility. The patient had a greater than 30-year cigarette smoking history. He denied history of neurologic disorder, gross hematuria, and renal calculus disease.

Urinalysis demonstrated microscopic hematuria with 10 erythrocytes per high-power field, 10 leukocytes per high-power field; test results for nitrite and leukocyte esterase were negative. Renal-bladder ultrasound did not reveal any abnormalities. Office cystoscopy revealed that the bladder had several irregular white lesions and irregular areas of raised mucosa, greatest over the right lateral and anterior wall of the bladder.

The patient was then brought to the operating room for bladder biopsies. Pathology revealed high-grade T1 urothelial carcinoma with CIS. The patient was counseled on options including re-resection, BCG, chemotherapy with radiation, and cystoprostatectomy. The patient was evaluated by the oncology service and was deemed a poor candidate for chemotherapy with radiation. He also adamantly refused cystoprostatectomy and, due to his diminished performance status, surgical recovery would be exceedingly challenging. Therefore, he elected BCG treatment with subsequent re-resection and bladder biopsies.

Upon administration of the BCG intravesically, the patient uncontrollably leaked the solution via the urethra. A Foley catheter was then placed and plugged in an attempt to keep the BCG in the bladder; however, the patient leaked the entire solution around the catheter. Due to his severe urge incontinence, he could not tolerate the instillation, even with maximal doses of antimuscarinic medication. Therefore, in an attempt to increase the patient's bladder capacity and decrease urge incontinence to allow for the BCG solution to remain in the bladder for the prescribed time, a strategy proposed was to perform intradetrusor injection of BoNT/A. Having been advised that this treatment could result in urinary retention, the patient agreed to this procedure and underwent injection of 200 units of BoNT/A into the detrusor. The 200 units of BoNT/A were diluted in normal saline without preservative (10 U/0.1 mL) and 20 injections were made, 7 into the bladder trigone. He subsequently began his first course of BCG 1 month later and was able to keep the solution in his bladder as prescribed for the entire 6-week course. The patient continued to void with a postvoid residual of approximately 75 mL.

After his first course of BCG, the patient underwent repeat bladder biopsies that showed persistent CIS and high-grade urothelial carcinoma. Therefore, he underwent repeat injection of BoNT/A to the bladder with subsequent successful administration of intravesical BCG therapy. Nevertheless, the patient still had persistent CIS on repeat bladder biopsy despite two courses of BCG. As such, the patient received a third treatment with intradetrusor BoNT/A in order to facilitate treatment with intravesical gemcitabine, as described by Sternberg and colleagues.[9]

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Discussion

The treatment of non–muscle-invasive bladder carcinoma is a challenging clinical situation in patients who are poor surgical candidates. Intravesical therapy, particularly BCG, has become the mainstay of treatment, predominantly in patients who cannot tolerate more aggressive therapy. In the patient presented here, however, intravesical treatment was not initially feasible due to his severe urge incontinence unresponsive to antimuscarinic medication. The strategy of injecting BoNT/A into the patient's bladder allowed for adequate dwell time for the BCG solution by alleviating detrusor overactivity with incontinence. Therefore, the use of intradetrusor BoNT/A proved to be

effective in allowing cancer treatment in this difficult scenario. To our knowledge, this is the first such case describing the use of BoNT/A in facilitating the treatment of bladder carcinoma.

The use of BoNT/A in detrusor overactivity is predicated on the notion that the toxin will have the same effect on the detrusor muscle as it does on skeletal muscle. Schurch and colleagues[8] illustrated that BoNT/A injection into the detrusor is an effective therapeutic option in patients with spinal cord injury and incontinence refractory to anticholinergic medication. In this series of 19 patients, 17 patients (89.5%) had continence restored after injection of 200 to 300 units of BoNT/A. Karsenty and associates[10] reviewed 18 clinical studies regarding the efficacy of BoNT/A in the treatment of neurogenic detrusor overactivity with urinary incontinence refractory of antimuscarinic medications. The review showed that 40% to 80% of patients attained full continence after treatment with BoNT/A, and there was a mean reduction in maximum detrusor pressure and improvement of quality of life. The efficacy of BoNT/A peaks between 1 and 4 weeks after injection, can last for 3 to 4 months on average, but does diminish with time.[11] Therefore, injections must be repeated to sustain effectiveness, yet generally do not show a decline in therapeutic effect with repeat injections. Injection of BoNT/A has been shown to provide significant improvement in the quality of life of patients with both neurogenic and idiopathic detrusor overactivity with decreased frequency, urgency, and number of urge incontinence episodes.[12]

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In general, injection of BoNT/A is well tolerated with minimal adverse events. The review by Karsenty and associates[10] showed that most common adverse events after BoNT/A injection are urinary tract infection, mild hematuria, and injection site pain. Urinary retention is another adverse effect that Shaban and Drake[13] have highlighted, by illustrating that some patients may require clean intermittent catheterization for the first time after BoNT/A injection and, therefore, have a significant impairment in their quality of life. As a result, a clear discussion regarding the risk of retention and proper teaching of clean intermittent catheterization is a necessity prior to initiating treatment.

In addition to BCG, other intravesical chemotherapy treatments and maintenance with agents such as gemcitabine, mitomycin, or doxorubicin may be feasible in a patient with severe urge incontinence after injection of BoNT/A. Further investigation is required to ensure safety and formulate an appropriate treatment algorithm for the use of BoNT/A in the setting of bladder dysfunction with concomitant bladder carcinoma. In essence, we report the use of BoNT/A in a patient with refractory urge incontinence that enables the treatment of superficial bladder carcinoma with intravesical BCG and gemcitabine. ■

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The authors report no real or apparent conflicts of interest.

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MAIN POINTS

- Botulinum neurotoxin type A (BoNT/A) has become a second-line therapy for neurogenic detrusor overactivity with urinary incontinence and overactive bladder in patients who are refractory to or intolerant of antimuscarinic therapy.
- The treatment of non–muscle-invasive bladder carcinoma is a challenging clinical situation in patients who are poor surgical candidates. The use of BoNT/A in detrusor overactivity is predicated on the notion that the toxin will have the same effect on the detrusor muscle as it does on skeletal muscle.
- In addition to Bacillus Calmette-Guérin, other intravesical chemotherapy treatments and maintenance with agents such as gemcitabine, mitomycin, or doxorubicin may be feasible in a patient with severe urge incontinence after injection of BoNT/A.

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