

Intravesical administration of combined hyaluronic acid and chondroitin sulfate can improve symptoms in patients with refractory bacillus Calmette-Guérin-induced chemical cystitis: Preliminary experience with one-year follow-up

Vittorio Imperatore¹, Massimiliano Creta², Sergio Di Meo¹, Roberto Buonopane¹, Nicola Longo², Ferdinando Fusco², Lorenzo Spirito², Ciro Imbimbo², Vincenzo Mirone²

¹ Unità Operativa di Urologia, Ospedale Buon Consiglio - Fatebenefratelli, Napoli, Italy;

² Clinica Urologica, Università Federico II di Napoli, Napoli, Italy.

Summary

Objective: We investigated the efficacy of intravesical instillations of combined

hyaluronic acid (HA) and chondroitin sulphate (CS) in patients with bacillus Calmette-Guérin (BCG)-induced chemical cystitis unresponsive to first-line therapies.

Patients and methods: We retrospectively reviewed the clinical records of patients with grade 2 BCG-induced chemical cystitis unresponsive to first line therapeutic options performed according to the International Bladder Cancer Group guidelines who underwent intravesical instillations of HA/CS. Bladder pain, urinary urgency, voiding volume and number of voids/24 hours recorded prior to treatment, at the end of the treatment, at six months and at one-year follow-up were recorded and analyzed. **Results:** The records of 20 patients were identified. All patients underwent eight weekly instillations of HA/CS. Mean baseline visual analogue scale (VAS) scores \pm Standard Deviation (SD) for urinary urgency and bladder pain were 7.8 ± 0.5 and 7.2 ± 1.0 , respectively. Mean number of voids/24 hours \pm SD was 15.4 ± 2.3 and mean urine volume per void \pm SD was 85.8 ± 21.0 mL. At the end of the treatment, mean VAS scores \pm SD for urgency and pain significantly decreased to 4.7 ± 1.1 and 4.2 ± 0.9 , respectively ($p < 0.05$ in both cases). Mean number of voids/24 hours \pm SD decreased to 9.6 ± 1.4 ($p < 0.05$) and mean urine volume per void \pm SD significantly increased to 194.1 ± 59.5 mL ($p < 0.05$). At six months and one-year follow-up, all outcome measures remained stable.

Conclusions: Bladder instillations of HA/CS provide significant and durable improvement of bladder pain, urinary urgency, urinary volume per void and urinary frequency in patients with refractory BCG-induced chemical cystitis.

KEY WORDS: Bacillus Calmette-Guérin; Bladder cancer; Chondroitin sulphate; Cystitis; Hyaluronic acid.

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INTRODUCTION

Intravesical immunotherapy with bacillus Calmette-Guérin (BCG) is the most effective prophylactic treatment for patients with non-muscle invasive bladder cancer (BCa) at intermediate and high risk of recurrence and/or progression after complete tumor removal (1). BCG-related toxicity is a great concern for these patients and it can occur locally and/or systemically (1). Chemical cystitis is the most common local side effect

and has been reported in up to 80% of patients (2-4). Histologically, BCG-induced chemical cystitis is characterized by an intense inflammatory reaction involving the lamina propria associated with nonspecific reactive atypia of the overlying urothelium that may be partially or entirely denuded (5). Clinically, it is characterized by storage lower urinary tract symptoms and hematuria with negative urine cultures. Reduced functional bladder capacity has been also reported. Most patients experience self-limiting symptoms that usually begin 2 to 4 hours after instillation and resolve rapidly over the next 24 to 48 hours (5). However, symptoms may persist or worsen and can become a troubling problem for some patients during BCG therapy and in the post-BCG observation period (5). The management of BCG-related side effects should reflect their type and grade and involves a stepwise approach according to the recommendations provided by the International Bladder Cancer Group (IBCG) (1, 6). First-line therapeutic options for patients with BCG-related cystitis include phenazopyridine, propantheline bromide or non-steroidal anti-inflammatory drugs (1, 6). If symptoms persist or worsen, guidelines recommend postponing therapy, perform a urine culture, and start empirical antibiotic therapy with subsequent adjustments in case of positive culture (1, 6). In cases of negative culture, quinolones and potentially analgesic anti-inflammatory instillations are recommended (1, 6-8). A defective glycosaminoglycan (GAG) barrier has recently emerged as the key factor in the pathogenesis of many pathophysiological processes that involve multiple biological systems including the bladder (i.e. biofilm formation, chemical and radiation damage) (9, 10). The GAGs best represented within the urothelial coating are hyaluronic acid (HA) and chondroitin sulfate (CS). The balanced association of HA and CS is indicated to treat chronic inflammatory diseases of the bladder originated from damage of the GAG layer of the bladder epithelium. Studies on bladder instillations of HA/CS as GAG replenishment therapy suggest that this formulation is efficacious in a wide range of clinical conditions characterized by chronic bladder inflammation including interstitial cystitis/painful bladder syndrome,

recurrent urinary tract infections, radiation cystitis (11, 12). To date, only few studies evaluated the benefits of bladder instillations with HA/CS in patients with chemical cystitis induced by BCG (8, 13). We aimed to investigate the efficacy of intravesical instillations of combined HA/CS in patients with BCG-induced chemical cystitis unresponsive to first-line treatments.

PATIENTS AND METHODS

The clinical records of patients with diagnosis of BCG-induced grade 2 chemical cystitis unresponsive to first line therapeutic options performed according to IBCG recommendations who underwent intravesical instillations of combined HA/CS between January 2010 to January 2015 were retrospectively reviewed (6). Grade 2 chemical cystitis was defined as severe and/or > 48 hours cystitis according to the *World Health Organization* grading scale (14). Patients with systemic side effects related to BCG, active genitourinary tract infections, actinic bladder, follow-up < 1 year, or incomplete data were excluded.

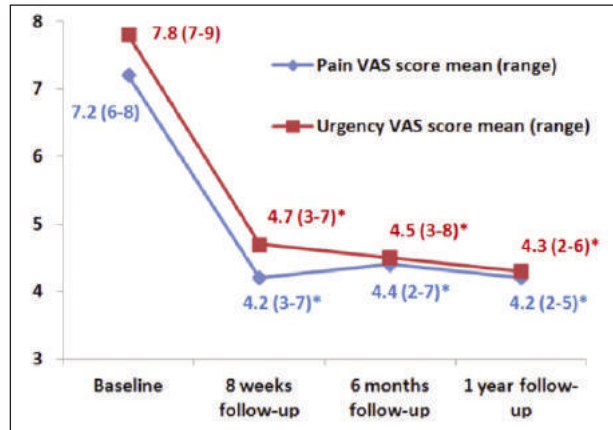
The followings were considered outcome measures: urinary urgency, bladder pain, urinary volume per void, number of voids/24 hours. Urinary urgency and bladder pain were investigated through a 0-10 visual analogue scale (VAS) score. Urinary volume per void and number of voids/24 hours were investigated through frequency/volume charts. Demographic and clinical data were collected including ethnicity, age, gender, tumor characteristics, previous therapies, symptoms onset, oncologic follow-up. For all outcome measures, values recorded at baseline, at the end of the treatment, at six months and one-year follow-up were collected and compared. Moreover, treatment related adverse event were also collected. Continuous variables were reported as mean, *standard deviations (SD)* and ranges. Categorical variables were reported as absolute values and percentages. Data were analyzed using the Student's t test, the Mann-Whitney and the Wilcoxon test, as appropriate. P values < 0.05 were considered statistically significant. Analyses were performed with SPSS version 17.0 (*SPSS Inc, Chicago, IL, USA*). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

A total of 20 Caucasian patients were identified who met the study criteria. Mean age was 61.8 years (range 48-77), 9 patients were males (45%) and 11 (55%) were females. BCa risk stratification revealed high- and intermediate-risk tumors in 14 and 6 patients, respectively. BCG-induced grade 2 chemical cystitis occurred after a mean of 3.5 instillations (range: 2-6). Symptoms persisted in all patients despite therapy with non-steroid anti-inflammatory drugs and quinolones. The treating physician decided to definitively stop BCG instillations in all cases. Patients were counseled about early cystectomy and refused. All patients received intravesical instillations of combined HA and CS (HA 1.6% 800 mg/50 mL and CS 2% 1000 mg/50 mL) weekly for eight weeks. All patients underwent follow-up investigations for BCa

Figure 1.

Mean Visual Analogue Scale (VAS) scores for symptoms of urinary urgency and bladder pain at baseline, at the end of the treatment (8 weeks), at six-months and at one-year follow-up. (*: p < 0.05 with respect to baseline).



according to recommendations provided by *European Urology Guidelines*. At baseline, mean VAS scores ± SD for bladder pain and urinary urgency were 7.2 ± 1.0 and 7.8 ± 0.5, respectively. while mean number of voids/24 hours ± SD, and mean urinary volume per void ± SD were 15.4 ± 2.3 and 85.8 ± 21.0 mL, respectively. At the end of the treatment (8 weeks), symptoms improved in all but one patient. Mean VAS scores ± SD for bladder pain and urinary urgency significantly decreased to 4.2 ± 0.9 and to 4.7 ± 1.1, respectively (Figure 1). Mean number of voids/24 hours ± SD, and mean urinary volume per void ± SD significantly improved to 9.6 ± 1.4 and 194.1 ± 59.5 mL, respectively (Figures 2 and 3). At six months follow up, mean VAS scores ± SD for bladder pain and urinary urgency were 4.4 ± 1.1 and 4.5 ± 1.0, respectively. Mean number of voids/24 hours ± SD, and mean urinary volume per void ± SD were 9.1 ± 1.6 and 210.8 ± 58.3 mL, respectively. At one year follow up, mean VAS scores ± SD for bladder pain and urinary urgency were 4.2 ± 0.8 and 4.3 ± 0.9,

Figure 2.

Mean number of voids/24 hours at baseline, at the end of the treatment (8 weeks), at six-months and at one-year follow-up. (*: p < 0.05 with respect to baseline).

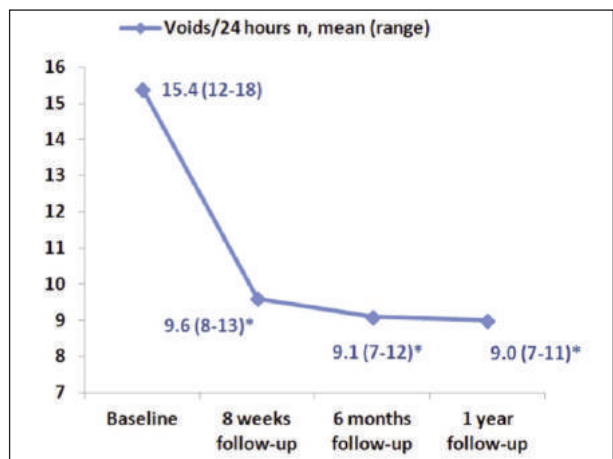
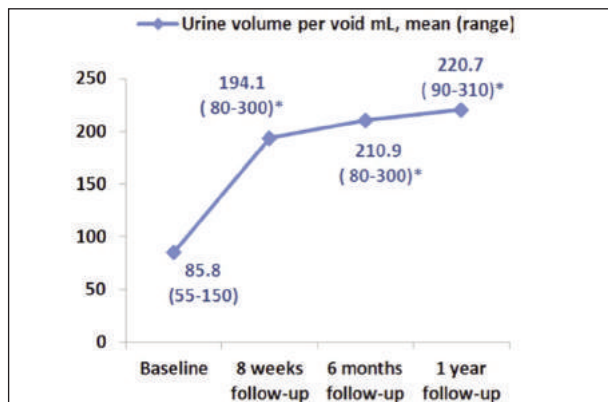


Figure 3. Mean urine volume per void at baseline, at the end of the treatment (8 weeks), at six-months and at one-year follow-up. (*: $p < 0.05$ with respect to baseline).



respectively. Mean number of voids/24 hours \pm SD, and mean urinary volume per void \pm SD were 9.0 ± 0.9 and 220.7 ± 55.3 mL, respectively (Figures 2 and 3).

Not statistically significant differences were evident when comparing values recorded at eight weeks, six months and one-year follow-up for all outcome measures. We did not observe any side effect due to the treatment. At one-year follow-up none of the patients had BCa recurrence.

DISCUSSION

BCa is the most common malignancy of the urinary tract, the seventh most common cancer in men and the 17th in women (1, 15-17). Transurethral resection of bladder tumors is the gold standard for removal of BCa, to allow diagnosis and, in many cases, definitive treatment (1, 15-17). However, tumor may recur or progress to muscle invasive disease and further adjuvant intravesical therapies are often needed (1). BCG intravesical immunotherapy is the most effective prophylactic management for BCa in situ as well as for Ta and T1 BCa at intermediate and high risk of recurrence and progression after complete transurethral resection (1). Morbidity secondary to intravesical BCG represents a great clinical concern. Toxicities requiring treatment discontinuation or interruption are frequently seen during the first year of therapy and chemical cystitis represents the most common local side effect (18, 19). Chemical cystitis is characterized by negative urine cultures and symptoms resemble to those of the urgency/frequency and painful bladder syndromes (8, 18). Symptoms are generally self-limited. However, they can persist or worsen in some cases (18). The IBCG published recommendations for the treatment of intravesical therapy-associated adverse events (6).

The management of BCG-related side-effects should reflect their type and grade and involves a stepwise approach (1). Analgesic and anti-inflammatory intravesical instillations are recommended as an adjunctive option for patients with symptoms of cystitis that persist despite first-line anti-inflammatory therapies (1, 6). To date, however, evidences about the efficacy of intravesical instillations in this clinical scenario are limited. Palou *et al.* treated 16 patients with severe BCG cystitis unresponsive to systemic medical treat-

ments with an anaesthetic anti-inflammatory solution administered by intravesical instillations (19). Authors obtained good results in 94% of the cases with immediate clinical improvement in terms of pain and urinary symptoms, and no side effects (19). Chuang *et al.* investigated, in a retrospective review, the potential utility of botulinum toxin A bladder injections in two patients with BCG-induced chemical cystitis who had failed conventional therapies (20). The Authors reported significant symptomatic improvements in both patients. The bladder capacity increased from 110 to 230 mL, urinary frequency decreased from 16 to 12 episodes per day, and using a 10-point visual analogue pain scoring system, the perceived pain score decreased from 8 to 2 (20). However, theoretical risks of the injection procedure of botulinum toxin A exist, including hematuria, perforation, urinary tract infections, and injection-site pain (20).

The role of GAG replenishment therapy in patients with chemical cystitis was investigated by Sommariva *et al.* (8). Authors evaluated the efficacy of intravesical instillations with sodium hyaluronate in 55 male patients with acute iatrogenic cystitis secondary to bladder chemo-immunostillation or pelvic radiotherapy. Of these, 17 patients received BCG. After 16 weeks VAS for pain improved in every case of chemical cystitis from an initial mean value of 8.6 to a final mean value of 1. Bladder capacity increased in all cases of chemical cystitis from a mean value of 56 mL to 276 mL. However, the study population was highly heterogeneous as 12 patients were treated with contemporary bladder hyperthermia. Moreover, patients also received dexamethasone intravesical (8). Results from the present study showed statistically significant improvements of bladder pain, urinary urgency, number of voids/24 hours and voided volume in patients with chemical cystitis secondary to intravesical immunotherapy with BCG and unresponsive to anti-inflammatory and quinolone therapies who received intravesical instillations of HA/CS. These results are in line with those reported by Sommariva *et al.* (8) Moreover, for the first time, we observed a persistence of benefits after treatment discontinuation up to one year. The rationale behind the clinical benefits of intravesical instillations of HA/CS in patients with diagnosis of chemical cystitis secondary to intravesical immunotherapy with BCG is unknown. However, some potential mechanisms can be hypothesized. Evidences exist suggesting that a defective urothelial barrier is involved in the pathogenesis of several chronic bladder conditions, such as interstitial cystitis/painful bladder syndrome, recurrent urinary tract infections, chemical and radiation cystitis (20). The surface of the urothelial cells carries a thick layer of glycoproteins and proteoglycans, together forming a GAG layer, which constitutes a hydrophilic mucosal coating and a barrier against solutes or noxious substances in the urine. A defect in this layer may be the first step in the development of urothelial dysfunction (9). Bladders lacking the apical layer of cells become more permeable, but impermeability can be restored with exogenous GAGs (21). Moreover, HA/CS may act in the context of chemical cystitis secondary to BCG by interfering with the inflammatory process. Indeed, studies have demonstrated that CS and HA may inhibit leukocyte migration, adherence of immune complexes, and binding to specific receptors (22). Moreover, reduction

of local production of proinflammatory cytokines has been also described (9). However, further studies are needed to specifically address these issues. Other Authors have investigated the benefits of GAG replenishment therapy in patients receiving BCG in a preventive setting. In their pilot study, *Topazio et al.* evaluated the role of the sequential administration of HA and BCG (22). Authors found significantly lower VAS scores for pain, number of daily micturiations, and *International Prostate Symptom Scores* in patients receiving HA and BCG with respect to patients receiving BCG alone (22). However, cost/benefits issues and potential interaction between BCG and HA deserve careful evaluations (22). Interestingly, none of the subjects in the present study had BCa recurrence at one-year follow-up despite BCG interruption. To date, little is known about the optimal treatment in patients with high-risk tumors who could not complete BCG instillations because of intolerance (1). Although GAG replenishment therapy may potentiate the protective barrier of the urothelium to prevent implantation of BCa tumor cells, the role of intravesical HA/CS in terms of BCa recurrence and progression is poorly understood and this issue deserves well designed pre-clinical and clinical studies (9). We acknowledge potential limitations of the present study. First, it was a retrospective study thus selection bias cannot be avoided. Moreover, the number of patients was low and there was not a control group. Therefore, formal randomized controlled trials and wider series are required to confirm these preliminary data and to draw definitive conclusions.

CONCLUSIONS

Intravesical instillations of HA/CS combination can improve urinary urgency, bladder pain, urinary frequency, and voided volume in patients with refractory BCG-induced chemical cystitis. Clinical benefits can persist up to one year after the suspension of the treatment.

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Correspondence

Vittorio Imperatore, MD (Corresponding Author)
 v.imperatore@alice.it
 Sergio Di Meo, MD - s.dimeo72@gmail.com
 Roberto Buonopane, MD - robertobuonopane@libero.it
 Unità Operativa di Urologia, Buon Consiglio Fatebenefratelli Hospital,
 Via A. Manzoni, 220, 80123, Napoli, Italy
 Massimiliano Creta, MD - max.creta@gmail.com
 Nicola Longo, MD - Ferdinando Fusco, MD - Lorenzo Spirito, MD
 Ciro Imbimbo, MD - Vincenzo Mirone, MD
 Clinica Urologica, Università Federico II di Napoli
 Via S.Pansini, 5, 80131 Napoli, Italy