



Adelmidrol + hyaluronic acid in the treatment of symptoms associated with intravesical anticancer therapy in non-muscle invasive bladder cancer. An observational retrospective investigation

Giorgio CANEPA, Fabio CAMPODONICO, Stefania TAMAGNO, Anna LA CAMERA, Carlo INTROINI

Struttura Complessa di Urologia, Ente Ospedaliero Ospedali Galliera, Genova, Italy

Citation: Canepa G, Campodonico F, Tamagno S, La Camera A, Introini C. Adelmidrol + hyaluronic acid in the treatment of symptoms associated with intravesical anticancer therapy in non-muscle invasive bladder cancer. An observational retrospective investigation. *Pelviperineology* 2023;42(1):5-11

ABSTRACT

Objectives: Intravesical therapy with Bacillus Calmette-Guérin and chemotherapy are an integral part in the management of non-muscle invasive bladder cancer (NMIBC), which is administered after transurethral surgical resection (TUR) of tumour to prevent relapse and progression of the disease. However, these therapies frequently cause side effects such as cystitis-like symptoms, which often can lead to treatment discontinuation. The purpose of this investigation was to evaluate the effect of intravesical administration of adelmidrol (AD) and hyaluronic acid (HA) on the typical symptoms in patients undergoing intravesical anticancer treatment for NMIBC, after TUR.

Materials and Methods: Thirty-one patients, who underwent TUR for NMIBC and had completed a cycle of intravesical anticancer treatment associated with AD + HA instillations, were considered for this retrospective investigation. For all patients, the main collected outcomes were: Pain intensity, urgency and discomfort related to frequent micturition (FM-related discomfort) evaluated by visual analogue scale, symptoms frequency and patient's degree of concern evaluated by pelvic pain and urgency/frequency patient symptom scale, and health-related quality of life detected with the 12-item short form survey.

Results: Intravesical instillation of AD + HA as an add-on treatment to intravesical anticancer therapy allowed to keep under control pain intensity, urgency and FM-related discomfort, enabling all patients to complete the entire course of anticancer treatment.

Conclusion: This retrospective investigation shows the potential efficacy of AD + HA to control anticancer treatment-related side effects. Larger randomized controlled studies are needed to confirm these encouraging results.

Keywords: Adelmidrol; chemotherapy; cystitis; hyaluronic acid; intravesical therapy; non-muscle invasive bladder cancer

Address for Correspondence: Giorgio Canepa, Struttura Complessa di Urologia, Ente Ospedaliero Ospedali Galliera, Genova, Italy

Phone: +39 3482633337 **E-mail:** giocanepa@libero.it **ORCID ID:** orcid.org/0000-0002-4970-6800

Received: 09 January 2023 **Accepted:** 23 March 2023

©Copyright 2023 by the International Society for Pelviperineology / Pelviperineology published by Galenos Publishing House.

INTRODUCTION

Intravesical therapy is an integral part in the management of non-muscle invasive bladder cancer (NMIBC), which is administered after transurethral surgical resection (TUR) of tumours, to prevent relapse and progression of the disease. Immunotherapy with Bacillus Calmette-Guérin (BCG) and chemotherapy with mitomycin C (MMC) or epirubicin (EPI), are the most used intravesical therapies.^{1,2} BCG is typically used for cancers with an intermediate or high risk of progression, while intravesical chemotherapy is usually adopted for cancers with a high risk of recurrence, but a low risk of progression.³⁻⁵ Both intravesical chemotherapy and BCG can lead to side effects of different degrees. The most frequent are cystitis-like symptoms such as urgency, dysuria, and increased micturition frequency. Often, these local side effects can lead to treatment discontinuation or incomplete treatment, resulting in suboptimal outcomes. Therefore, prevention and management of side effects are paramount to ensure oncologic treatment efficacy.^{1,3}

The complex symptomatology provoked by intravesical therapy with BCG, MMC or EPI chemotherapy, is the consequence of inflammatory processes. Particularly intense and/or persistent traumatic, chemical, hormonal, infectious, and iatrogenic stimuli, led to the progressive impairment of the urothelial structure due to mast cells (MCs) activation.⁶ Activated MCs can directly interact with other cells of the immune system and guide the inflammatory reaction promoting vascular permeability, local tissue response and the recruitment of various inflammatory mediators.⁷ Inappropriate and persistent MCs stimulation can transform the local and acute inflammatory response into a chronic and systemic inflammatory disease, with amplification of painful stimuli too.^{8,9} Therefore, an approach based on MCs modulation could be effective in counteracting intravesical therapy-related side effects.

With this aim, adelmidrol (AD), a derivative of azelaic acid, could represent a possible therapeutic strategy. AD is in fact able to keep MCs normal reactivity, through its capacity to increase the endogenous levels of the natural MCs modulator: Palmitoylethanolamide (PEA).¹⁰⁻¹⁴ The beneficial effects of AD

were already demonstrated in acute and chronic inflammation, as well as in patients with chronic interstitial cystitis/bladder pain syndrome (IC/BPS).^{15,16}

The purpose of this investigation was to evaluate the efficacy of intravesical administration of a product containing AD in combination with hyaluronic acid (HA)¹⁷⁻²², in counteracting antitumor therapy-related side effects.

MATERIALS AND METHODS

This manuscript reports the data collected at the Urology Outpatient Clinic of the Galliera Hospital (Genova, Italy) between October 2019 and November 2021, on the clinical practice adopted in patients starting the 1st cycle of intravesical therapy after TUR of NMIBC.

The approach used was to perform intravesical instillations with a medical device combining AD 2% + HA 0.1% (Vessilen®, Epitech Group SpA) in add-on to antitumor therapy with BCG, EPI or MMC.

AD + HA posology was decided on the base of a previous similar experience reported in literature.¹⁶ Data were collected at the evaluation times normally performed at the urology clinic. Therapeutic scheme and follow-up times are reported in Figure 1.

Ethics committee approval and patients written informed consent were obtained for data publication.

Outcomes collected were: 1) Pain, urgency and discomfort related to frequent micturition (FM-related discomfort) by Visual Analogue Scale (VAS). VAS score ranges from 0 mm to 10 mm, with higher score representing higher symptoms intensity;²³ 2) Frequency of cystitis-like symptoms and patients concern by pelvic pain and urgency/frequency patient symptom (PUF) scale. PUF-Total score is the sum of “PUF-symptom” and “PUF-both” scores. Total score ranges from 0 to 35, with higher score representing worst condition;²⁴ 3) Health-related quality of life with 12-item short form (SF-12) survey. SF-12 evaluates both the physical (PCS) and the mental (MCS) components. Total score ranges from 0 to 100, with higher score indicating better health.²⁵ Intensity of pain, urgency and FM-related discomfort

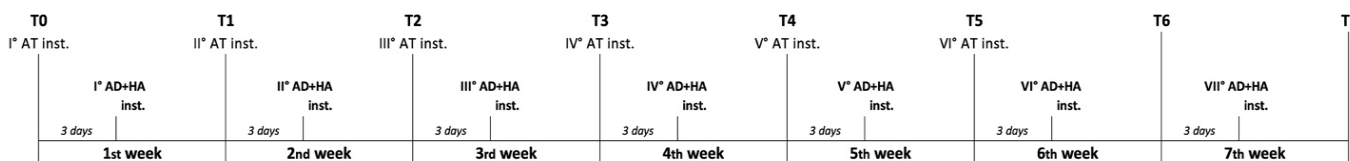


Figure 1. Treatment scheme and evaluation time points
AT: antitumor therapy; inst.: instillation

were evaluated weekly from T0 to T7. PUF and SF-12 were completed by patients before the start (T0) and at the end (T7) of AD + HA treatment.

Beside these evaluations, it was performed a descriptive analysis of the percentage of patients who experienced local side effects over the entire observation period: VAS pain or urgency intensity score ≥ 5 was considered representative of clinically significant side effects. This value includes intensity between moderate and severe and it was established arbitrarily as a symptom threshold above which the continuation of anticancer therapy could be compromised.²⁶ As FM-related discomfort was not a symptom but a bother, and therefore very subjective, it was not possible to establish a reliable cut-point for this parameter. Alternatively, the combination between answers to question n°1 “How many times do you go to the bathroom during the day?” and question n°2a “How many times do you go to the bathroom at night?” of the PUF scale was considered for this analysis at T0 and T7 (time points at which the PUF was administered). Voiding frequency was considered normal if both scores of PUF questions n°1 and n°2a were 0-1, while it was considered altered with a score >1 at one and/or both questions.²⁴

Statistical Analysis

Statistical analysis was performed using the generalized linear mixed model considering three different time points: the beginning of the anticancer therapy (T0) (3 days before the start of AD + HA therapy), the end of the anticancer therapy (T5), and the last control after the end of AD + HA administration (T7). Post-hoc analyses were performed with the correction of Tukey-Kramer for multiple comparisons. Variables such as gender, age, tumour staging and type of intravesical anticancer therapy were included in the model as covariates. A *p*-value of less than 0.05 was considered significant. All scores are given as mean \pm standard error, unless otherwise specified.

RESULTS

Thirty-one patients (13 female and 18 males) with a mean age of 71 years old, treated with AD + HA instillations in addition to intravesical anticancer therapy after TUR for NMIBC, were considered in this retrospective investigation. Anticancer treatment was performed with intravesical instillations of BCG in 71%, MMC in 10% and EPI in 19% of cases. All demographics and patients baseline characteristics are reported in Table 1.

Pain intensity, urgency and FM-related discomfort significantly decreased over time. Pain intensity decreased from 1.5 ± 0.48 (T0) to 1.4 ± 0.42 (T5) reaching 0.4 ± 0.18 (T7) (T0-T5-T7 *p*=0.01; T0-T5 n.s.; T5-T7 *p*=0.01) (Figure 2A). None of the considered

covariates had any significant influence on treatment efficacy. Urgency decreased from 3.0 ± 0.66 (T0) to 2.1 ± 0.58 (T5) reaching 1.5 ± 0.44 (T7) (T0-T5-T7 *p*=0.01; T0-T5 n.s.; T5-T7 n.s.) (Figure 2B). Urgency increased with age (*p*=0.03). FM-related discomfort decreased from 3.3 ± 0.56 (T0) to 3.0 ± 0.50 (T5) reaching 2.2 ± 0.46 (T7) (T0-T5-T7 *p*=0.007; T0-T5 n.s.; T5-T7 *p*=0.007) (Figure 2C). Gender influenced FM-related discomfort, with women having a greater discomfort (*p*=0.03).

At the end of analgesic treatment (T7) average values of the PUF-total score were indicative of a significant improvement of patients concern (*p*=0.04). In particular, the PUF-symptoms score showed a significant improvement over time, moving from a mean value of 5.4 ± 0.54 (T0) to 4.4 ± 0.47 (T7) (*p*=0.01); PUF-bothers score showed a reduction from T0, passing from a value of 2.9 ± 0.05 (T0) to 2.5 ± 0.43 (T7) (n.s.) (Figure 3). None of the covariates significantly affected neither the symptoms nor the bother score.

SF-12 PCS changed from 48.7 ± 1.53 (T0) to 50.4 ± 1.45 (T7) (n.s.). SF-12 MCS moved from 52.1 ± 1.57 (T0) to 51.0 ± 1.58 (T7) (n.s.).

The percentage of patients who experienced symptoms of pain intensity and/or urgency with VAS ≥ 5 was 35% (T0), decreased to 23% (T5) and to 13% at the end of AD + HA treatment (T7) (Table 2). In particular, percentage of patients who experienced pain intensity with a VAS score ≥ 5 was 16% (T0), decreased to 10% (T5) and 3% (T7), while percentage of patients who experience urgency with a VAS score ≥ 5 was 32% (T0), decreased to 23% (T5) and 13% (T7) (Table 2). Percentage of patients with altered daily voiding frequency (according to questions n°1 and n°2a of the PUF scale) decreased from 77% (T0) to 68% (T7) (Table 3).

Table 1. Patient demographic data and baseline characteristics

| | |
|--|------------|
| Age (mean \pm S.D.) | 71 \pm 6 |
| Gender n (%) | |
| Male | 18 (58) |
| Female | 13 (42) |
| Stage of cancer n (%) | |
| TAHG | 12 (39) |
| TALG | 4 (13) |
| T1HG | 13 (42) |
| T1HG CIS | 2 (6) |
| Anticancer therapy n (%) | |
| BCG | 22 (71) |
| MMC | 3 (10) |
| EPI | 6 (19) |
| S.D.: standard deviation; BCG: Bacillus Calmette-Guérin; MMC: mitomycin C; EPI: epirubicin | |

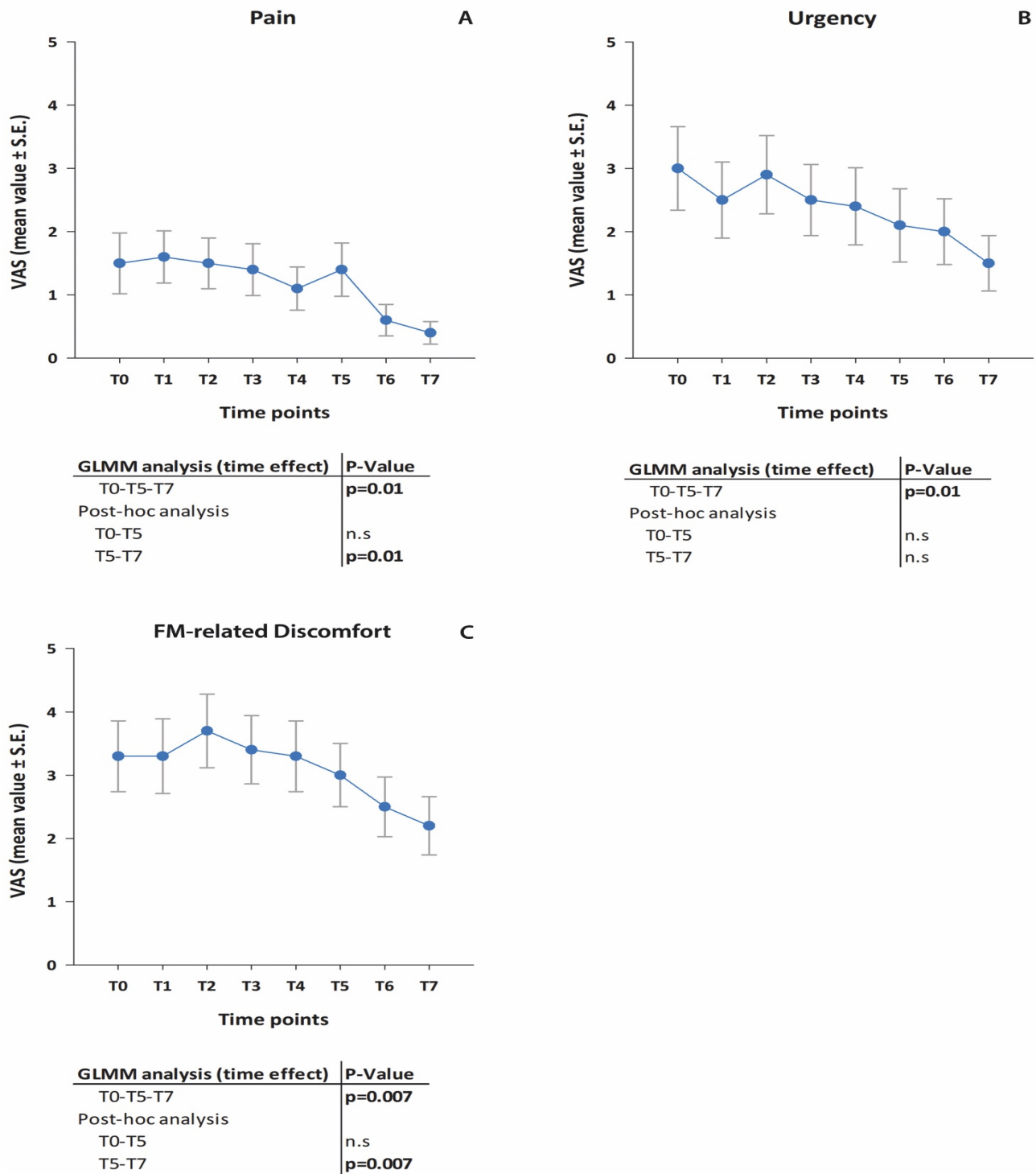


Figure 2. Changes over time in pain intensity, urgency and FM-related discomfort evaluated by VAS at the different evaluation time points
 Data are expressed as mean ± S.E.
 Intensity of pain (A), urgency (B) and FM-related discomfort (C) decreased significantly over time (T0-T5-T7 $p < 0.05$). Post-hoc analysis results are shown in the figure
 S.E.: standard error; n.s.: not significant

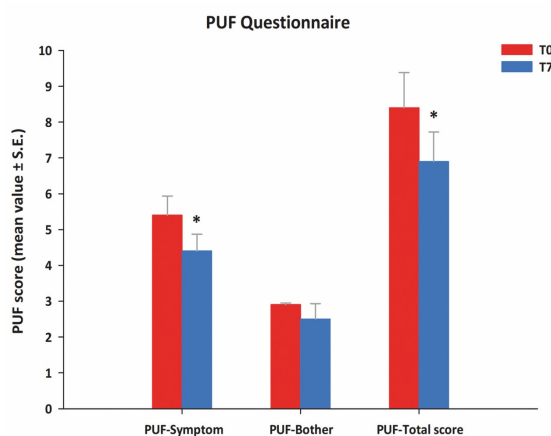
Table 2. Percentage of patients with clinically significant pain intensity and urgency at the different evaluation time points

| Symptoms | NRS scores | Percentage of patients | | | | | | | |
|-------------------------------|------------|------------------------|------|------|------|------|------|------|------|
| | | T0 | T1 | T2 | T3 | T4 | T5 | T6 | T7 |
| | | n=31 | n=31 | n=31 | n=31 | n=30 | n=31 | n=31 | n=31 |
| Pain intensity | ≥5 | 16% | 13% | 10% | 10% | 6% | 10% | 3% | 3% |
| Urgency | ≥5 | 32% | 23% | 29% | 29% | 27% | 23% | 16% | 13% |
| Pain intensity and/or urgency | ≥5 | 35% | 26% | 32% | 32% | 29% | 23% | 16% | 13% |

Table 3. Percentage of patients with normal or altered voiding frequency at baseline (T0) and the end of AD + HA treatment (T7)

| Daily voiding frequency | Percentage of patients | |
|--|------------------------|------------|
| | T0 n=31 | T7 n=31 |
| Patients with normal frequency (score 0-1 on both questions 1 and 2a of PUF questionnaire) | 23% | 32% |
| Patients with altered frequency (score >1 on question 1 and/or 2a of PUF questionnaire) | 77% | 68% |

PUF: patient symptom; AD: adelmidrol; HA: hyaluronic acid

**Figure 3.** Symptom frequency and patient bother evaluated by PUF scale at baseline (T0) and at the end of AD + HA treatment (T7)

Data are expressed as mean ± S.E.

PUF-total score and PUF-symptom score significantly improved between T0 and T7 ($p < 0.05$); PUFbother score showed a slight reduction (*n.s.*)

* $p < 0.05$; S.E.: standard error; *n.s.*: not significant; PUF: patient symptom

No patient discontinued treatment prematurely and there was no change in therapeutic scheme established.

DISCUSSION

Intravesical chemotherapy with MMC or EPI and immunotherapy with BCG are adjuvant therapies widely used after TUR to prevent recurrence and progression of bladder cancer.^{4,5}

Despite their great efficacy, these therapies have several local side effects such as the onset of urgency, dysuria, and increased micturition frequency, that lead to treatment delay or reduction in 55-83% of cases, and even to its interruption in 30%.^{21,27,28} Finding a new strategy to manage these side effects is therefore paramount to ensure oncologic treatment efficacy.^{1,3}

AD is a compound able to increase PEA endogenous levels.^{10,12,14} Oral administration of PEA in its micronized (m-PEA) and ultramicronized (um-PEA) forms already demonstrated to be effective in increasing intravesical anticancer therapy tolerability and improving pain in patients with BPS, thanks to its ability to modulate MCs degranulation.^{29,30} Likewise, instillations of AD together with HA (Vessilen®, Epitech Group Spa), led to a significant improvement of pain, urgency and frequency in patients suffering from chronic IC/BPS or other urothelial dysfunction.¹⁶

In this retrospective study, AD + HA instillations were introduced from the beginning of the 1st cycle with BCG, MMC/EPI, when the expected frequency of side effects is higher.

Overall, AD + HA allowed to keep under control intensity of pain, urgency and FM-related discomfort, enabling all patients to complete the entire cycle of adjuvant anticancer treatment.

Moreover, the continuation of AD + HA treatment after the end of anticancer cycle, led to a further improvement of symptomatology (reduction of VAS score and percentage of patients with side effects).

In particular, patients with at least one cystitis-like symptom from moderate to severe intensity (VAS score ≥5) were 35% at

T0, reduced to 23% at T5 and to 13% at T7. PUF total score at the end of AD + HA therapy reported a significant improvement in symptoms and of their impact on patients' life ("PUF-symptom" and "PUF-bother" scores respectively). Consistently with these results, no substantial differences were observed in SF-12 questionnaire for either PCS or MCS, from T0 to T7.

All patients completed the therapeutic scheme established and no patient reported side effects related to AD + HA.

In the analysed population, pain, urgency, FM-related discomfort means VAS scores and PUF basal scores were relatively low compared to literature data.^{20,22} This occurred because in the statistical analysis it was considered each patient treated with AD + HA, including those with no, or mild side effects. However, it is relevant to point out that many of these patients had no side effects at all, or showed only mild symptoms throughout the entire course of treatment.

Adding AD + HA could seem burdensome, taking account of the already high costs of chemo-immuno-prophylaxis. However, it has to be considered the lack of anticancer therapy discontinuation, together with the reduction of radical cystectomies number, and of further endoscopic bladder surgical treatments need.

Furthermore, despite the increased number of catheterizations, there were no infectious manifestations such as fever or macrohematuria, thus highlighting the absence of negative aspects in adding AD + HA to current clinical practice.

These are very preliminary results, on a small number of patients, lacking of a control group. A prospective, randomized and controlled study is required to optimize treatment protocol and confirm these promising data. It would be furthermore appropriate to evaluate the use of AD + HA during the 2nd cycle of anticancer treatment, a period equally subjected to side effects onset. Follow-up data are not yet available, but their collection is in progress, to confirm the absence of long-term consequences of AD + HA add-on, on the oncologic follow-up.

CONCLUSION

This retrospective observational study supports the introduction into clinical practice of AD + HA for the management of oncologic patients, in order to reduce anticancer treatment-related side effects and allow, as much as possible, the adherence to the established therapeutic protocol.

ACKNOWLEDGMENTS

The authors are grateful to EPITECH Group SpA for the information support, in particular to Francesco Puglisi, Area Manager Liguria.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of Liguria-Italy (Register no: 399/2022-DB id 12315). The study was conducted in accordance with the principles of Helsinki Declaration.

Informed Consent: Retrospective study. Written informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Contributions

Surgical and Medical Practices: G.C., F.C., C.I.; Concept: G.C.; Design: G.C., S.T.; Data Collection or Processing: S.T., A.L.C.; Analysis or Interpretation: G.C., F.C.; Literature Search: G.C.; Writing: G.C.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Witjes JA, Palou J, Soloway M, et al. Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy-Associated Adverse Events. *Eur Urol Suppl* 2008; 7: 667-74.
2. Babjuk M, Burger M, Compérat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. *Eur Urol* 2019; 76: 639-57.
3. Mathes J, Todenhöfer T. Managing Toxicity of Intravesical Therapy. *Eur Urol Focus* 2018; 4: 464-7.
4. Shen Z, Shen T, Wientjes MG, O'Donnell MA, Au JLS. Intravesical treatments of bladder cancer: review. *Pharm Res* 2008; 25: 1500-10.
5. PDQ Adult Treatment Editorial Board. Bladder Cancer Treatment (PDQ®): Health Professional Version. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002. Available on: <http://www.ncbi.nlm.nih.gov/books/NBK65962/>
6. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation. *Biochim Biophys Acta* 2012; 1822: 21-33.
7. Kinet JP. The essential role of mast cells in orchestrating inflammation. *Immunol Rev* 2007; 217: 5-7.
8. Zuo Y, Perkins NM, Tracey DJ, Geczy CL. Inflammation and hyperalgesia induced by nerve injury in the rat: a key role of mast cells. *Pain* 2003; 105: 467-79.
9. Skaper SD, Facci L. Mast cell-glia axis in neuroinflammation and therapeutic potential of the anandamide congener palmitoylethanolamide. *Philos Trans R Soc Lond B Biol Sci* 2012; 367: 3312-25.

10. Petrosino S, Puigdemont A, Della Valle MF, et al. Adelmidrol increases the endogenous concentrations of palmitoylethanolamide in canine keratinocytes and down-regulates an inflammatory reaction in an in vitro model of contact allergic dermatitis. *Vet J Lond Engl* 2016; 207: 85-91.
11. Petrosino S, Iuvone T, Di Marzo V. N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities. *Biochimie* 2010; 92: 724-7.
12. Cerrato S, Brazis P, Della Valle MF, Miolo A, Puigdemont A. Inhibitory effect of topical adelmidrol on antigen-induced skin wheal and mast cell behavior in a canine model of allergic dermatitis. *BMC Vet Res* 2012; 8: 230.
13. Noli C, Miolo A. The mast cell in wound healing. *Vet Dermatol* 2001; 12: 303-13.
14. Abramo F, Salluzzi D, Leotta R, et al. Mast cell morphometry and densitometry in experimental skin wounds treated with a gel containing adelmidrol: a placebo controlled study. *Wounds Compend Clin Res Pract* 2008; 20: 149-57.
15. Impellizzeri D, Di Paola R, Cordaro M, et al. Adelmidrol, a palmitoylethanolamide analogue, as a new pharmacological treatment for the management of acute and chronic inflammation. *Biochem Pharmacol* 2016; 119: 27-41.
16. Ostaro E, Impellizzeri D, Cervigni M, et al. Adelmidrol + sodium hyaluronate in IC/BPS or conditions associated to chronic urothelial inflammation. A translational study. *Pharmacol Res* 2018; 134: 16-30.
17. Poggi M, Johnstone P, Conner R. Glycosaminoglycan content of human bladders. a method of analysis using cold-cup biopsies. *Urol Oncol* 2000; 5: 234-7.
18. Morales A, Emerson L, Nickel JC. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *Urology* 1997; 49: 111-3.
19. Parsons CL. Epithelial coating techniques in the treatment of interstitial cystitis. *Urology* 1997; 49: 100-4.
20. Huang W, Wang F, Wu C, Hu W. Efficacy and safety of pirarubicin combined with hyaluronic acid for non-muscle invasive bladder cancer after transurethral resection: a prospective, randomized study. *Int Urol Nephrol* 2015; 47: 631-6.
21. Sommariva ML, Sandri SD, Guerrer CS. [Treatment of acute iatrogenic cystitis secondary to bladder chemo-immuno-instillation or pelvic radiotherapy]. *Urologia* 2010; 77: 187-92.
22. Topazio L, Miano R, Maurelli V, et al. Could hyaluronic acid (HA) reduce Bacillus Calmette-Guérin (BCG) local side effects? Results of a pilot study. *BMC Urol* 2014; 14: 64.
23. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983; 17: 45-56.
24. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002; 60: 573-8.
25. Ware J, Kosinski M, Keller S. SF-12: How to score the SF-12 Physical and Mental Summary Scales, 2nd edn. Boston, MA: The Health Institute, New England Medical Center, 1995.
26. Boonstra AM, Schiphorst Preuper HR, Balk GA, Stewart RE. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. *Pain* 2014; 155: 2545-50.
27. Koch GE, Smelser WW, Chang SS. Side Effects of Intravesical BCG and Chemotherapy for Bladder Cancer: What They Are and How to Manage Them. *Urology* 2021; 149: 11-20.
28. van der Meijden APM, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV, EORTC Genito-Urinary Tract Cancer Group. Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur Urol* 2003; 44: 429-34.
29. Di Cristina L, Accardo AM, Travagliato MG, Angileri M, Pizzardi N, Baruzza V. Ultramicrosized Palmitoylethanolamide in the treatment of painful symptoms associated with intravesical anti-cancer therapy in bladder carcinoma. *Pathos* 2018; 25.
30. Sommariva M, Schievano C, Saleh O. Micronized palmitoylethanolamide reduces bladder chronic pelvic pain due to different etiologies and improves bladder functions. *Pelviperineology* 2017; 36: 92-6.