









Communication

Treating BCG-Induced Cystitis with Combined Chondroitin and Hyaluronic Acid Instillations in Bladder Cancer

Renate Pichler ^{1,*} , Johannes Stäblein ¹, Andrea Mari ² , Luca Afferi ³ , David D'Andrea ⁴, Gautier Marcq ⁵ , Francesco del Giudice ⁶ , Francesco Soria ⁷, Jorge Caño-Velasco ⁸, José Daniel Subiela ⁹ , Andrea Gallioli ¹⁰, Karl H. Tully ¹¹, Keiichiro Mori ^{4,12}, Achim Herms ¹³, Benjamin Pradere ¹⁴ , Marco Moschini ¹⁵, Laura S. Mertens ¹⁶ and Martin Thurnher ¹⁷  on behalf of the European Association of Urology-Young Academic Urologists (EAU-YAU): Urothelial Carcinoma Working Group

- ¹ Department of Urology, Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, 6020 Innsbruck, Austria; johannes.staebelin@tirol-kliniken.at
- ² Unit of Oncologic Minimally-Invasive Urology and Andrology, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, 50134 Florence, Italy; andreamari08@gmail.com
- ³ Department of Urology, Luzerner Kantonsspital, 6000 Luzern, Switzerland; luca.afferi@gmail.com
- ⁴ Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, 1090 Vienna, Austria; morikeiichiro29@gmail.com (K.M.)
- ⁵ Department of Urology, Claude Huriez Hospital, CHU Lille, 59000 Lille, France
- ⁶ Department of Maternal Infant and Urologic Sciences, Policlinico Umberto I Hospital, 'Sapienza' University of Rome, 00185 Rome, Italy; francesco.delgiudice@uniroma1.it
- ⁷ Urology Division, Department of Surgical Sciences, University of Studies of Torino, 10124 Turin, Italy; francesco.soria@unito.it
- ⁸ Department of Urology, Gregorio Marañón University Hospital, 28007 Madrid, Spain; jorcavel@gmail.com
- ⁹ Department of Urology, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, 28034 Madrid, Spain; jdsubiela@gmail.com
- ¹⁰ Department of Urology, Fundació Puigvert, Autonomous University of Barcelona, 08193 Barcelona, Spain; andrea.gallioli@gmail.com
- ¹¹ Department of Urology and Neurourology, Marien Hospital Herne, Ruhr-University Bochum, 44625 Herne, Germany; karlh.tully@gmail.com
- ¹² Department of Urology, The Jikei University School of Medicine, Tokyo 105-8461, Japan
- ¹³ Neuro-Urology Unit, Department of Urology, Medical University of Innsbruck, 6020 Innsbruck, Austria; achim.herms@tirol-kliniken.at
- ¹⁴ Department of Urology, La Croix du Sud Hospital, 31130 Quint-Fonsegrives, France; benjaminpradere@gmail.com
- ¹⁵ Department of Urology, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, 20132 Milan, Italy; marco.moschini87@gmail.com
- ¹⁶ Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands; ls.mertens@gmail.com
- ¹⁷ Immunotherapy Unit, Department of Urology, Medical University of Innsbruck, 6020 Innsbruck, Austria; martin.thurnher@i-med.ac.at
- * Correspondence: renete.pichler@i-med.ac.at; Tel.: +43-(0)-512-504-24811; Fax: +43-(0)-512-504-28365



Citation: Pichler, R.; Stäblein, J.; Mari, A.; Afferi, L.; D'Andrea, D.; Marcq, G.; del Giudice, F.; Soria, F.; Caño-Velasco, J.; Subiela, J.D.; et al. Treating BCG-Induced Cystitis with Combined Chondroitin and Hyaluronic Acid Instillations in Bladder Cancer. *J. Clin. Med.* **2024**, *13*, 2031. <https://doi.org/10.3390/jcm13072031>

Received: 14 March 2024
Revised: 27 March 2024
Accepted: 30 March 2024
Published: 31 March 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: In non-muscle invasive bladder cancer, Bacillus Calmette–Guérin (BCG) responders benefit from strong Th1-type inflammatory and T cell responses mediating tumor rejection. However, the corresponding lack of anti-inflammatory Th2-type immunity impairs tissue repair in the bladder wall and facilitates the development of cystitis, causing urinary pain, urgency, incontinence, and frequency. Mechanistically, the leakage of the glycosaminoglycan (GAG) layer enables an influx of potassium ions, bacteria, and urine solutes towards the underlying bladder tissue, promoting chronic inflammation. Treatments directed towards re-establishing this mucopolysaccharide-based protective barrier are urgently needed. We discuss the pathomechanisms, as well as the therapeutic rationale of how chondroitin and hyaluronic acid instillations can reduce or prevent BCG-induced irritative bladder symptoms. Moreover, we present a case series of five patients with refractory BCG-induced cystitis successfully treated with combined chondroitin and hyaluronic acid instillations.

Keywords: BCG; bladder cancer; cystitis; hyaluronic acid; chondroitin; intravesical instillations

1. Introduction

Intravesical instillations with *Bacillus Calmette–Guérin* (BCG) are part of the success story of cancer immunotherapy for more than forty years [1]. BCG applications are still the standard adjuvant treatment in high-risk, non-muscle-invasive bladder cancer [2]. Repetitive intravesical BCG applications induce a local immune response that ultimately translates into an increased immune responsiveness termed trained immunity [3]. Consequently, intravesical BCG has not only local but also systemic effects.

BCG-induced cystitis is the most commonly reported local side effect of BCG treatment, and patients have the same symptoms as in non-BCG, bacterial urinary tract infections [4]. Irritative bladder symptoms are described in about 30–60% of cases, and patients complain of urgency, urinary frequency, nocturia, hematuria, and pain in the bladder region [4]. Interestingly, the rate of side effects showed no differences in age, BCG strains, or maintenance schedule [5–7]. The management of BCG-induced cystitis is clearly recommended in stages by current guidelines [2], including the discontinuation of the instillations and empirical antibiotic treatment, then anti-tuberculosis drugs with corticosteroids if the symptoms persist or, finally, a radical cystectomy in the case of contracted bladder or refractory symptoms. However, many patients show persistent symptoms which lead to a reduced quality of life (QoL) leading to the discontinuation of BCG treatment [2,8].

2. T Helper (Th) Cells in BCG-Induced Antitumor Effects and Bladder Inflammation and Repair

BCG enters the bladder wall at the tumor resection site through complexes with fibronectin [9]. Then, antigen-presenting cells in the urothelium phagocytose the BCG and present BCG-derived antigens to CD4⁺ T helper (Th) cells, which produce either Th1-type or Th2-type cytokines [10]. A local inflammatory immune response with an influx of granulocytes and mononuclear cells and the potent production of pro-inflammatory Th1 cytokines is associated with the BCG response [11]. During bladder infections, CD4⁺ Th cells, cytotoxic T cells, and $\gamma\delta$ T cells are recruited into the bladder to mediate antitumor immune responses. In contrast, the Th2 T cells mainly serve to repair the tissue damage in the bladder wall induced by bacterial infections and the Th1-type responses. Upon repair, the intact urothelium is able to restore the glycosaminoglycan (GAG) layer [12]. Thus, Th cell subsets play an essential role not only in BCG-induced antitumor activity but also in the subsequent bladder tissue repair (Figure 1).

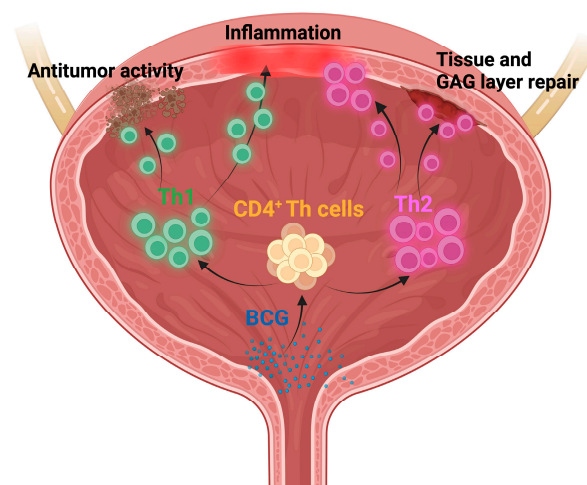


Figure 1. T helper (Th) cells in BCG-induced antitumor effects and bladder inflammation and repair. Intravesical application of BCG induces recruitment of CD4⁺ Th cells into the urothelium. A Th1-dominant

bladder microenvironment is needed for an effective antitumor response. However, BCG-induced Th1-type inflammation also promotes cystitis. In contrast, Th2 T cells are required to repair the bladder wall and to restore the glycosaminoglycan (GAG) layer [12].

3. Physiological Function of the GAG Layer and the Rationale of Treating BCG-Induced Cystitis with Intravesical Instillations of GAG Components

The GAG layer is a protective mucus layer over the urothelium with a specific permeability, which protects the bladder wall as a physical barrier. When the GAG layer is depleted during bladder infections, interstitial cystitis, transurethral bladder cancer resection, or intravesical treatments with BCG, the GAG deficiency results in a “leaky” epithelium, allowing the passage and influx of potassium ions, bacteria, and urine solutes towards the bladder tissue, initiating an inflammatory reaction in the bladder wall, thus promoting bladder symptoms such as urgency, frequency, and pain. Since the GAG layer mainly consists of hyaluronic acid, chondroitin sulfate, keratin sulfate, and heparin sulfate, reconstructing the dysfunctional GAG layer by instilling components of the GAG layer into the bladder appears to be a promising therapeutic concept (Figure 2).

Mechanistically, hyaluronic acid can restore the bladder GAG layer by altering epithelial permeability through stimulating the expression of tight junction proteins and by inducing anti-inflammatory mechanisms including the inhibition of mast cell activation and immune cell infiltration [13]. Analyses about the function of specific sulfated GAGs in the bladder has shown that endogenously produced chondroitin sulfate is the dominant sulfated GAG on the urothelial luminal surface, underlining its importance in the bladder barrier function [14]. Therefore, combined instillations of hyaluronic acid and chondroitin (iAluRil) seem to be a reasonable novel therapeutic approach in different bladder diseases resulting from urothelial GAG loss. One instillation consists of 40 mL of sodium hyaluronic 1.6% and chondroitin sulfate 2% in normal saline. iAluRil is applicated intravesically once a week for 8 weeks, then as further needed. Focusing on interstitial cystitis, the first small case series has already shown a good therapeutic efficacy of combined chondroitin and hyaluronic acid instillations (iAluRil) with a significant improvement in bladder symptoms and improved long-term outcomes over a 3-year period [15–17].

In BCG-treated bladder cancer patients, instillations of hyaluronic acid can serve two purposes: (a) to restore the physical barrier and to prevent irritative bladder symptoms, and (b) to increase antitumor activity in BCG-refractory bladder tumors, when hyaluronic acid is combined with paclitaxel in therapeutic bioconjugates (ONCOFID-P-B) [18]. ONCOFID-P-B instillations confirm a homogeneous distribution over the whole internal surface of the bladder mucosa with a low or absent systemic absorption resulting in low toxicity rates [18]. In addition, ONCOFID-P-B applied by intravesical instillations in BCG-refractory carcinoma in situ (CIS) showed very promising results in a phase I study [19]. A follow-up trial by Hurle et al. confirmed a high rate of complete responders (CR) in 75% of patients when administered weekly for up to 12 consecutive weeks, maintaining CR in 40% of patients after 15 months of follow-up [20].

Focusing on BCG-induced cystitis, Imperatore et al. reported a case series of 20 patients with refractory BCG-induced cystitis showing a significant and durable improvement of bladder pain, urgency, and frequency through bladder instillations of chondroitin and hyaluronic acid [21]. In detail, the mean (SD) visual analogue scale (VAS) score for urinary urgency and bladder pain decreased from 7.8 (0.5) and 7.2 (1.0) at baseline to 4.7 (1.1) and 4.2 (0.9) at the end of the intravesical chondroitin and hyaluronic acid instillations. All outcome measures remained stable at 6 months and at a 1-year follow-up [21]. However, all studies on the treatment of BCG-related cystitis included only a small number of patients with a high heterogeneity concerning follow-up, BCG strains, BCG schedules, and clinical endpoints.

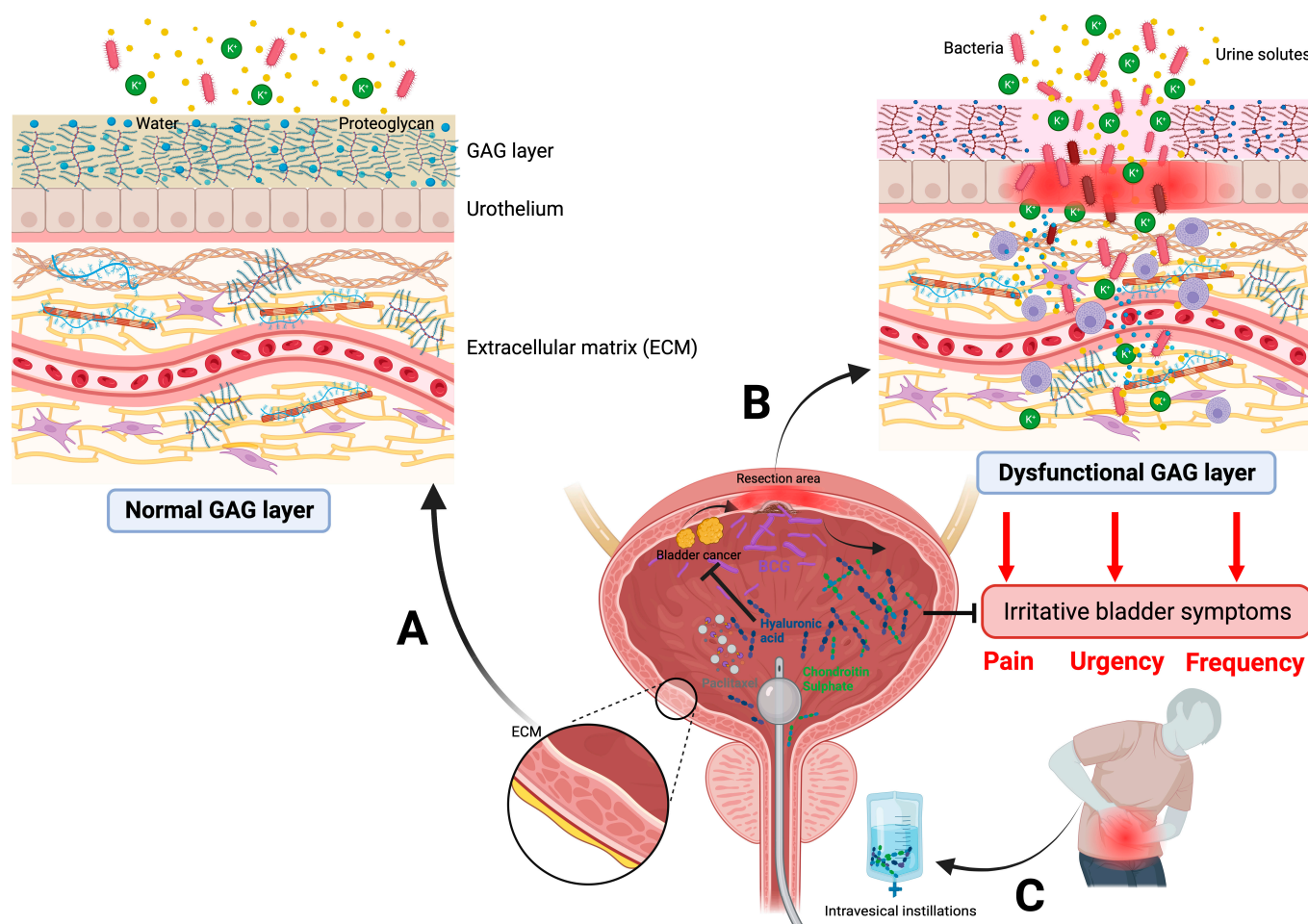


Figure 2. Physiological function and dysregulation of the glycosaminoglycan (GAG) layer. (A) In physiological conditions, the protective bladder wall lining, consisting of GAGs including hyaluronic acid, chondroitin sulfate, heparin sulfate, and keratin sulfate, protects the bladder and prevents the adhesion of urine solutes and bacteria. (B) Damage to this GAG layer is triggered not only by bladder infections but also by bladder tumor surgery or intravesical instillation treatments. As a consequence, the penetration of urine molecules into the bladder tissue results in an inflammatory process, which leads to the activation of mast cells. Then, cytokines, histamine, proteolytic enzymes, and vasoactive amines are released, resulting in a pro-inflammatory response in the urothelium resulting in extracellular matrix degradation. Patients complain of bladder pain, urgency, and frequency. (C) Intravesical instillations of hyaluronic acid and chondroitin serve to re-establish the epithelial integrity. The initial data also suggest an antitumor effect of hyaluronic acid in combination with paclitaxel in BCG-refractory tumors [19,20].

4. Methods

After approval by the local ethics committee (study number 1006/2017), the medical records of patients with primary, high-risk NMIBC and consecutive intravesical BCG therapy after a transurethral resection of the bladder (TURB) were reviewed retrospectively. BCG-induced cystitis was defined as persistent irritative bladder symptoms with repetitive negative urine cultures. A second TURB within 3–6 weeks after the initial resection was performed in all patients to exclude a residual tumor or understaging. According to the EAU guidelines [2], intravesical BCG induction therapy was given in a 6-weekly schedule once a week, followed by maintenance therapy for 1–3 years (3-weekly once a week at 3, 6, 9, 12, 18, 24, 30, and 36 months). Each intravesical instillation through a sterile disposable catheter contained 2×10^8 to 3×10^9 viable units from a live attenuated strain of BCG bacteria seed RIVM derived from seed 1173-P2 (BCG Medac, Wedel, Germany). Each solution

was retained up to 1–2 h. The BCG-induced cystitis was treated with combined intravesical chondroitin and hyaluronic acid instillations. Evaluating the frequency, severity, and impact on the QoL of patients, two questionnaires—the Incontinence Questionnaire—Urinary Incontinence Short Form (ICIQ-UI SF) and the Incontinence Quality of Life questionnaire (I-QoL)—were collected dynamically at different time points (at baseline and at 6, 12, and 24 weeks) during/after chondroitin and hyaluronic acid instillations. Oncologic surveillance was performed with a cystoscopy and a urinary (voided urine and bladder washing) cytology every 3 months for a period of 2 years, then every 6 months for 5 years, and once every year thereafter [2]. Computed tomography urography was performed initially at the time of diagnosis and repeated once a year. A muscle-invasive bladder cancer detected during a follow-up (progression) or a high-grade relapse after the BCG therapy was defined as BCG failure.

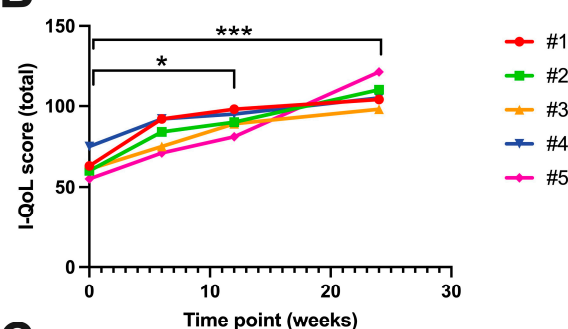
5. Results

Here, we provide a further case series of five patients with refractory BCG-induced cystitis treated with combined hyaluronic acid and chondroitin instillations. iAluRil was instilled once a week for 6 weeks. The mean (range) age was 64.2 (56–75) years. Three (60%) of the five patients were male. All patients were defined as BCG responders with no tumor recurrence during a mean oncological follow-up of 36.5 months. All patients confirmed a primary high-risk NMIBC. In four of the five patients, the BCG-induced cystitis occurred during the BCG maintenance therapy. In detail, the mean (range) onset of irritative bladder pain symptoms was 332.4 (7–947) days after starting the intravesical BCG treatment (Figure 3A). In all patients, a significant improvement of incontinence and irritative symptoms was already noticed 6 weeks after the beginning of chondroitin and hyaluronic acid instillations. Focusing on QoL, the mean (SD) IQoL score was improved from 62.8 (7.4) at baseline to 82.8 (9.6) at 6 weeks (Figure 3B). The mean (SD) ICIQ-UI-SF score decreased from 10.4 (4.7) at baseline to 4.8 (1.9) at 6 weeks after starting the combined chondroitin and hyaluronic acid instillations (Figure 3C). A detailed overview of the descriptive characteristics and questionnaire outcomes are presented in Figure 3.

A

Characteristics	Total (N = 5)
Age [years], mean (SD)	64.2 (8.2)
Male sex, n (%)	3 (60%)
Tumor stage, n (%)	
pTa	2 (40%)
pT1	3 (60%)
Concomitant CIS, n (%)	2 (40%)
Tumor grade, n (%)	
High-grade	5 (100%)
Onset of BCG-induced cystitis after first BCG instillation [days], mean (range)	332.4 (7–947)
Occurrence of BCG-induced cystitis, n (%)	
During BCG induction	1 (20%)
During BCG maintenance	4 (80%)
ICIQ-UI-SF score, mean (SD)	
Baseline	10.4 (4.7)
Week 6	4.8 (1.9)
Week 12	2.0 (1.0)
Week 24	0.8 (0.4)
IQoL score, mean (SD)	
Baseline	62.8 (7.4)
Week 6	82.8 (9.6)
Week 12	90.6 (6.5)
Week 24	107.6 (8.6)

B



C

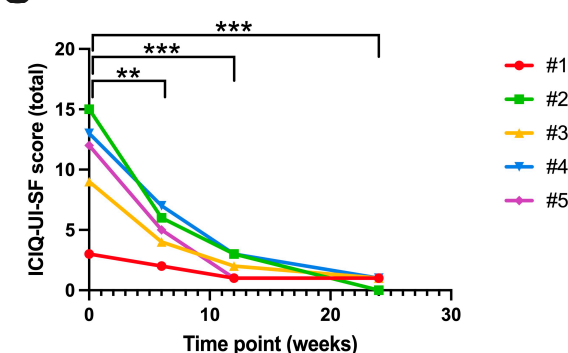


Figure 3. Retrospective case series of five patients with an overview of (A) the descriptive and histopathological characteristics, as well as (B,C) questionnaire outcomes. Both the I-QoL (B) and

ICIQ-UI-SF (C) questionnaires were evaluated at baseline and at 6, 12, and 24 weeks after the start of chondroitin and hyaluronic acid instillation therapy in patients with persistent BCG-induced cystitis. * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$; repeated measures ANOVA.

6. Limitations

One of the major limitations of the present case series is the heterogeneous and retrospective character of the limited patient number, which restricts the statistical methods of interpretation. Therefore, further prospective and multi-institutional randomized trials with sufficient statistical power and long-term follow-ups are required to validate these preliminary findings.

7. Conclusions and Future Perspectives

In summary, different inflammatory bladder diseases, including BCG-induced cystitis, are linked in the first step of the disease to the deficiency of the mucous layer of the GAG, with a limited ability to repair the damaged urothelial layer and to restore the GAG. The early repair of the GAG layer can be supported by the intravesical application of the components of the GAG, such as hyaluronic acid and chondroitin sulfate, preventing chronic bladder inflammation. Further prospective randomized studies with larger numbers of cases are needed to confirm this very promising preliminary data.

Author Contributions: Conceptualization, R.P., J.S., L.S.M. and M.T.; data curation, J.S., A.M., L.A., D.D., G.M., F.d.G., F.S., J.C.-V. and J.D.S.; investigation, J.S., A.M., F.S., J.C.-V. and J.D.S.; supervision, A.M., D.D., G.M., F.d.G., F.S., K.H.T., B.P., M.M., L.S.M. and M.T.; writing—original draft, R.P., J.S., L.S.M. and M.T.; writing—review and editing, R.P., J.S., A.M., L.A., D.D., G.M., F.d.G., F.S., J.C.-V., J.D.S., A.G., K.H.T., K.M., A.H., B.P., M.M., L.S.M. and M.T. All authors have read and agreed to the published version of this manuscript.

Funding: This study received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the Medical University of Innsbruck (study number 1006/2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Morales, A.; Eidinger, D.; Bruce, A.W. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J. Urol.* **1976**, *116*, 180–183. [[CrossRef](#)]
2. Babjuk, M.; Burger, M.; Capoun, O.; Cohen, D.; Compérat, E.M.; Dominguez Escrig, J.L.; Gontero, P.; Liedberg, F.; Masson-Lecomte, A.; Mostafid, A.H.; et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *Eur. Urol.* **2022**, *81*, 75–94. [[CrossRef](#)] [[PubMed](#)]
3. Van Puffelen, J.H.; Keating, S.T.; Oosterwijk, E.; van der Heijden, A.G.; Netea, M.G.; Joosten, L.A.B.; Vermeulen, S.H. Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer. *Nat. Rev. Urol.* **2020**, *17*, 513–525. [[CrossRef](#)] [[PubMed](#)]
4. Lamm, D.L.; Stogdill, V.D.; Stogdill, B.J.; Crispin, R.G. Complications of bacillus Calmette-Guérin immunotherapy in 1278 patients with bladder cancer. *J. Urol.* **1986**, *135*, 272–274. [[CrossRef](#)] [[PubMed](#)]
5. van der Meijden, A.P.; Sylvester, R.J.; Oosterlinck, W.; Hoeltl, W.; Bono, A.V. 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*, 429–434. [[CrossRef](#)] [[PubMed](#)]

6. Oddens, J.R.; Sylvester, R.J.; Brausi, M.A.; Kirkels, W.J.; van de Beek, C.; van Andel, G.; de Reijke, T.M.; Prescott, S.; Alfred Witjes, J.; Oosterlinck, W. Increasing age is not associated with toxicity leading to discontinuation of treatment in patients with urothelial non-muscle-invasive bladder cancer randomised to receive 3 years of maintenance bacille Calmette-Guérin: Results from European Organisation for Research and Treatment of Cancer Genito-Urinary Group study 30911. *BJU Int.* **2016**, *118*, 423–428.
7. Unda-Urzaiz, M.; Cozar-Olmos, J.M.; Miñana-Lopez, B.; Camarero-Jimenez, J.; Brugarolas-Rossello, X.; Zubiaur-Libano, C.; Ribal-Caparro, M.J.; Suarez-Charneco, A.J.; Rodriguez-Tesedo, V.; Chantada-Abal, V.; et al. Safety and efficacy of various strains of bacille Calmette-Guérin in the treatment of bladder tumours in standard clinical practice. *Actas. Urol. Esp. (Engl. Ed.)* **2018**, *42*, 238–248. [[CrossRef](#)] [[PubMed](#)]
8. Witjes, J.A.; Palou, J.; Soloway, M.; Lamm, D.; Brausi, M.; Spermon, J.R.; Persad, R.; Buckley, R.; Akaza, H.; Colombel, M.; et al. Clinical practice recommendations for the prevention and management of intravesical therapy-associated adverse events. *Eur. Urol. Suppl.* **2008**, *7*, 667. [[CrossRef](#)]
9. Zhao, W.; Schorey, J.S.; Bong-Mastek, M.; Ritchey, J.; Brown, E.J.; Ratliff, T.L. Role of a bacillus Calmette-Guérin fibronectin attachment protein in BCG-induced antitumor activity. *Int. J. Cancer* **2000**, *86*, 83–88. [[CrossRef](#)]
10. Atkins, H.; Davies, B.R.; Kirby, J.A.; Kelly, J.D. Polarisation of a T-helper cell immune response by activation of dendritic cells with CpG-containing oligonucleotides: A potential therapeutic regime for bladder cancer immunotherapy. *Br. J. Cancer* **2003**, *89*, 2312–2319. [[CrossRef](#)]
11. Pichler, R.; Gruenbacher, G.; Culig, Z.; Brunner, A.; Fuchs, D.; Fritz, J.; Gander, H.; Rahm, A.; Thurnher, M. Intratumoral Th2 predisposition combines with an increased Th1 functional phenotype in clinical response to intravesical BCG in bladder cancer. *Cancer Immunol. Immunother.* **2017**, *66*, 427–440. [[CrossRef](#)]
12. Wu, J.; Abraham, S.N. The Roles of T cells in Bladder Pathologies. *Trends Immunol.* **2021**, *42*, 248–260. [[CrossRef](#)] [[PubMed](#)]
13. Boucher, W.S.; Letourneau, R.; Huang, M.; Kempuraj, D.; Green, M.; Sant, G.R.; Theoharides, T.C. Intravesical sodium hyaluronate inhibits the rat urinary mast cell mediator increase triggered by acute immobilization stress. *J. Urol.* **2002**, *167*, 380–384. [[CrossRef](#)]
14. Janssen, D.A.; van Wijk, X.M.; Jansen, K.C.; van Kuppevelt, T.H.; Heesakkers, J.P.; Schalken, J.A. The distribution and function of chondroitin sulfate and other sulfated glycosaminoglycans in the human bladder and their contribution to the protective bladder barrier. *J. Urol.* **2013**, *189*, 336–342. [[CrossRef](#)]
15. Cervigni, M.; Natale, F.; Nasta, L.; Padoa, A.; Voi, R.L.; Porru, D. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. *Int. Urogynecol. J. Pelvic. Floor Dysfunct.* **2008**, *19*, 943–947. [[CrossRef](#)]
16. Porru, D.; Leva, F.; Parmigiani, A.; Barletta, D.; Choussos, D.; Gardella, B.; Daccò, M.D.; Nappi, R.E.; Allegri, M.; Tinelli, C.; et al. Impact of intravesical hyaluronic acid and chondroitin sulfate on bladder pain syndrome/interstitial cystitis. *Int. Urogynecol. J.* **2012**, *23*, 1193–1199. [[CrossRef](#)]
17. Cervigni, M.; Natale, F.; Nasta, L.; Mako, A. Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: Long-term treatment results. *Int. Urogynecol. J.* **2012**, *23*, 1187–1192. [[CrossRef](#)] [[PubMed](#)]
18. Tringali, G.; Lisi, L.; Bettella, F.; Renier, D.; Di Stasi, S.M.; Navarra, P. The in vitro rabbit whole bladder as a model to investigate the urothelial transport of anticancer agents The ONCOFID-P paradigm. *Pharmacol. Res.* **2008**, *58*, 340–343. [[CrossRef](#)] [[PubMed](#)]
19. Bassi, P.F.; Volpe, A.; D’Agostino, D.; Palermo, G.; Renier, D.; Franchini, S.; Rosato, A.; Racioppi, M. Paclitaxel-hyaluronic acid for intravesical therapy of bacillus Calmette-Guérin refractory carcinoma in situ of the bladder: Results of a phase I study. *J. Urol.* **2011**, *185*, 445–449. [[CrossRef](#)]
20. Hurle, R.; Guazzoni, G.; Colombo, P.; Santoro, A.; De Cobelli, O.; Trapani, E.D.; Nohales, G.; Carlos, L.; Duran-Merino, R.; Lazzeri, M. Oncofid-P-B: A novel treatment for BCG unresponsive carcinoma in situ (CIS) of the bladder: Results of a prospective European Multicentre study at 15 months from treatment start. *Urol. Oncol.* **2022**, *40*, e9–e11. [[CrossRef](#)]
21. Imperatore, V.; Creta, M.; Di Meo, S.; Buonopane, R.; Longo, N.; Fusco, F.; Spirito, L.; Imbimbo, C.; Mirone, V. 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. *Arch. Ital. Urol. Androl.* **2018**, *90*, 11–14. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.