Original Study

Bladder Instillation Therapy With Hyaluronic Acid and Chondroitin Sulfate Improves Symptoms of Postradiation Cystitis: Prospective Pilot Study

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Abstract

In this study, we evaluate the efficacy of hyaluronic acid and chondroitin sulfate instillation in men with symptomatic cystitis after radiation therapy for PCa. Of a total of 80 patients treated with RT for PCa, 30 of these reported LUTS and received instillation therapy for 1 year. HA-CS significantly reduced overall LUTS and bother as measured by the ICSI/ICPI questionnaire.

Background: After radiotherapy (RT) for prostate cancer (PCa), several patients reported lower urinary tract symptoms (LUTS) due to damage and discontinuation of the glycosaminoglycan layer of the bladder. Instillation of hyaluronic acid and chondroitin sulfate (HA-CS) represents replenishment therapy of the glycosaminoglycan layer. The aim of the study is to evaluate the efficacy and safety of HA-CS in men with symptomatic cystitis after RT for PCa. **Materials and Methods:** Eighty consecutive men were treated with RT for PCa; 30 of these (37.5%) reported clinically relevant LUTS and associated bother as measured by the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI) Questionnaire 3 months after RT. Symptomatic patients received instillation therapy with HA-CS weekly for the first month and then at weeks 6, 8, and 12. All patients completed the ICSI/ICPI questionnaire before and after RT and at the end of HA-CS treatment. **Results:** HA-CS significantly reduced postradiation LUTS ($P < .001$) and bother ($P = .006$). Age, Gleason score, and radiation dose were the main determinants of worsening of LUTS after radiation (ICSI score baseline vs. postradiation: $P = .047$, .043, and .023). In multivariate analysis, only age influenced LUTS worsening after RT ($P = .01$). Age, radiation dose, and radiation toxicity were related to recovery of LUTS (ICSI score postradiation vs. post–HA-CS $P = .041$, $P = .050$, and $P = .046$). In multivariate analysis, no factor was statistically significant. **Conclusions:** A remarkable worsening of symptoms and bother was observed after RT. HA-CS instillation is a safe treatment and resulted in an improvement of LUTS irrespective of age and clinical features, with full recovery of urinary bother.

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Introduction

Radical prostatectomy and radiotherapy (RT) are both effective treatments for clinically localized prostate cancer (PCa).[1] In selected cases, RT can be recommended as primary treatment[2] or as adjuvant or salvage treatment after radical prostatectomy.[3] In the last decades, the technique of RT has substantially improved to spare surrounding tissue, but even contemporary modifications, such as intensity-modulated RT with releasing the maximum dose on the prostate but lesser dose on adjacent organs (eg, the urinary bladder), cause lower urinary tract symptoms (LUTS) in up to 50% of men

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treated with doses > 70 Gy. These patients frequently report dysuria, urgency, frequency, nocturia, or pelvic pain.[4,5] LUTS after RT for PCa usually are summarized as "post-radiation cystitis"[6] and can have a negative impact on quality of life (QoL), including vitality or social and physical performance.[7] In addition to QoL deterioration, LUTS and associated bother also may result in remarkable direct and indirect costs for the health care system and society. It was estimated only for the symptom nocturia that the direct annual costs for the assessment and treatment of nighttime falls and fractures are as high as $1.5 billion in the United States and €1 billion in the 15 largest countries of the European Union. Indirect costs of nocturia due to loss of work productivity were estimated to be approximately $62.5 billion per year in the United States and €29 billion in the 15 largest countries of the European Union.[8]

During the last decade, several preclinical studies focused on the pathogenetic mechanisms of postradiation cystitis. It was hypothesized that RT induces damage, disruption, and, consequently, discontinuation of the glycosaminoglycan (GAG) layer of the bladder mucosa, resulting in leakage of potassium ions into the interstitial space of the bladder wall and activation of C-fibers.[9,10] C-fiber activation also results in the release of Substance P, which can promote a neuroinflammatory cascade with activation of mast cells and subsequent release of histamines.[9,10] These mechanisms are thought to cause LUTS, especially urgency, frequency nocturia, and pain.

The pathways involved in postradiation cystitis suggest that replenishment of the GAG layer could reduce neurogenic inflammation and prevent subepithelial mast cell activation. Many substances have been investigated for the treatment for postradiation cystitis, including chondroitin sulfate (CS), hyaluronic acid (HA), heparin, and pentosanpolysulfate.[11]

HA, a proteoglycan present in the GAG layer of the bladder urothelium in healthy subjects, has an inhibitory function on mast cell degranulation, whereas CS promotes regeneration of the GAG layer.[12] Because of the different mechanisms of action, the combination of HA and CS appears to be an appealing alternative to monotherapy. However, few clinical trials have investigated this combination treatment for LUTS or bladder pain. All published trials on HA-CS combination therapy analyzed patients with interstitial cystitis or bladder pain syndrome, whereas no evidence exists in patients with postradiation cystitis. Therefore, the aim of the present pilot study was to evaluate the efficacy and safety of intravesical GAG replenishment treatment with HA-CS combination in men with LUTS or bladder pain syndrome after RT for PCa.

Materials and Methods

Study Population and Study Design

Between May 2012 and April 2014, all men affected by LUTS or bladder pain after RT for PCa were enrolled in this prospective, observational pilot study carried out in a tertiary referral center. All patients have been treated according to European Association of Urology guidelines. Inclusion criteria were (1) diagnosis of localized PCa, (2) RT as primary or adjuvant treatment, (3) postradiation cystitis as measured by the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI) questionnaire 3 months after RT (ICSI $\geq$ 1 and ICPI $\geq$ 3),[4] capability to read and answer self-reported questionnaires, and (5) signed informed consent. Men with a history of acute urinary retention or bladder catheterization, recurrent and persistent urinary tract infections, bladder stones, known malignant diseases besides PCa, and those without worsening of LUTS and bother after RT (delta baseline vs. postradiation ICSI/ICPI $\leq$ 0) were excluded from the study. Age and comorbidities, clinical stage, Gleason score, radiation dose, and toxicity were recorded. No patients receive androgen deprivation therapy as neoadjuvant therapy or primary therapy, according to European guidelines.

Three months after RT, all patients with postradiation cystitis (ICSI $\geq$ 1, ICPI $\geq$ 3, and delta baseline vs. postradiation ICSI/ICPI > 0) were treated with transurethral instillation according to instructions and schedules reported in the package leaflet of the manufacturer and our intern protocol of HA-CS weekly for the first month and afterward at weeks 6, 8, and 12. The severity of LUTS and bother were assessed by the ICSI/ICPI questionnaire 3 times during the study: before RT (baseline), 3 months after RT, and 2 weeks after the last HA-CS instillation (week 14).

The study protocol was approved by the local ethics committee of the hospital. The study did not require any deviation of the current Good Clinical Practice standards for RT for PCa and was conducted in accordance with the principles of the Declaration of Helsinki.

Radiotherapy Protocol

The planning computed tomography scan was performed with 3-mm slices, with the patient in the supine position and using a leg immobilization system (Combifix-Sinmed, Civco, Kalona, IA). The dose was applied at the isocenter according to the International Commission of Radiation Units and Measurements Recommendations. Standardized conventional fractionation was used in all patients: 2 Gy/fraction, 5 fractions weekly, and total radiation dose 66 to 70 Gy. RT was delivered with a 4-field technique and 10 to 18 MV photons. The clinical target volume was limited to the prostatic bed and periprostatic tissue, ensuring adequate coverage of the vesico-urethral anastomosis. The planning treatment volume included the clinical target volume plus a 10-mm margin in all directions. Consequently, 66 to 70 Gy were delivered in 33 to 35 fractions with a tridimensional conformal technique.

Hyaluronic Acid and Chondroitin Sulfate Instillation

In all patients, transurethral bladder instillations were performed according to the instructions and schedules reported in the package leaflet of the manufacturer (Ialuril, IbsaPambio-Noranco, Switzerland). In brief, HA and CS were diluted in 50 mL physiologic saline solution (HA 1.6% [800 mg/50 mL] plus CS 2% [1000 mg/50 mL]) placed inside the bladder with a lubricated sterile 14F-catheter and retained for at least 1 hour.

ICSI/ICPI Questionnaire

The validated O'Leary et al[13] ICSI/ICPI questionnaires were used to assess symptoms and bother related to RT.[13] These questionnaires initially intended to measure only the outcome of bladder pain syndrome/interstitial cystitis but have become a widely accepted tool to identify LUTS and associated bother in general.[14] Therefore, the ICSI/ICPI questionnaires also can measure LUTS and associated bother caused by RT. The ICSI questionnaire