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THE ROLE OF INTRAVESICAL GLYCOSAMINOGLYCANS IN TOXICITY INDUCED BY ADJUVANT INTRAVESICAL THERAPY: GENETIC LABORATORY EVIDENCE

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Introduction and Objectives: The intravesical administration of hyaluronic acid and chondroitin sulphate solution (HA-CS) has been proven active in patients affected by interstitial cystitis (1). The gene expression of fibronectin (*FN*) in bladder washings has recently been correlated with local toxicity of adjuvant intravesical therapy (2). The aim of the study was to investigate the genetic evidence of the healing or protective action that HA-CS could carry out also in patients suffering from topical toxicity induced by intravesical adjuvant therapy given for non-muscle invasive bladder cancer. *Materials and Methods:* The study included 50 patients submitted to adjuvant intravesical therapy with mitomycin, epirubicin or bacillus Calmette–Guérin (BCG). Ten age-matched healthy patients were enrolled as control group. Before, during and after intravescical therapy, bladder washing samples were collected to investigate the gene expression of *FN*. In 9 more patients the samples were collected also immediately before and a week after the instillation of HA-CS. Topical toxicity was classified into 3 grades: 0-1, light (no medical therapy); 2, moderate (medical therapy); 3, severe (instillation postponed). Bladder washing samples were analyzed by isolation of cellular RNA using a miRNeasy Mini Kit (Qiagen®). RT-PCR was performed in order to analyze *FN* gene expression. Changes in the *FN* content were calculated using the ΔΔCt method after normalization with endogenous reference 18s rRNA and calibrating Ct value for each RNA obtained for triplicate reactions. Statistical analysis was performed to correlate the *FN* gene expression to tumor characteristics, treatment, topical toxicity and intravesical administration of HA-CS. *Results: FN* median value before the adjuvant treatment was 1.1-fold, with higher levels in patients with multiple tumors (median *FN*=1.5; mean=3.9; p=0.0003). Twenty patients (34%) showed grade 2-3 toxicity. Compared to controls (*FN*=1), *FN* increased during therapy a median of 4-fold (range=0.2-45.2; mean=7.5) in presence of grade 2-3 toxicity, remaining stable in asymptomatic patients (median *FN*=0.6; range=0.1-3.2), with a statistically significant difference (p=0.0005). In 9 patients, one week after single instillation of HA-CS, the median *FN* gene expression decreased from 3.2 to 0.33 with concomitant symptomatic relief. *Discussion and Conclusion:* Fibronectin is a fundamental element for the repair of urothelial damage. *FN* gene is probably activated by the need of fibronectin for healing process and down-regulated by the integrity of bladder urothelium. In our preliminary experience *FN* gene expression in bladder washings resulted strictly related to local toxicity induced by intravesical therapy. It increases after transurethral resection (TUR) of multiple tumors due to the greater urothelial damage. It increases also during intravesical therapy reaching the highest levels in case of severe toxicity due to the extensive urothelial damage. A single instillation of intravesical hyaluronic acid and chondroitin sulphate solution induces a rapid reduction of *FN* gene expression levels, particularly when high levels are present. The *FN* gene down-regulation induced in patients with toxicity is due to intravesical therapy and might represent an objective and measurable indicator of the healing activity of intravesical instillation of HA-CS.

1 Van Agt S *et al*: Treatment of interstitial cystitis by intravesical instillation of hyaluronic acid: A prospective study on 31 patients, Prog Urol *21*: 218-225, 2011.

2 Serretta V *et al*: Fibronectin (FN), Epidermal Growth Factor-Receptor (EGF-R) and Heparin-Binding Epidermal Growth Factor-like Growth Factor (HB- EGF) urinary expression and topical toxicity of adjuvant intravesical therapy for non muscle invasive bladder cancer (NMI-BC). 28th EAU Congress, Stockholm, 2014. Eur Urol Suppl *13*: e409, 2014.

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COMPARISON OF OPEN AND LAPAROSCOPIC RADICAL NEPHRECTOMY IN RENAL TUMORS WITH SIZE ≥10 CM

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Introduction: Laparoscopic radical nephrectomy (LRN) is considered standard of care for T1 renal tumors not amenable to nephron-sparing surgery. The role of LRN in the management of very large renal masses has yet to be determined. Few recent publications showed that LRN could also be performed for large renal tumors. Indications are now expanding to include patients with T2 or T3 tumors. Ritchie and colleagues (1) emphasized that patients within T2 stage