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Can we decrease the acute proctitis in prostate cancer patients using hyaluronic acid during radiation therapy: a prospective historically controlled clinical study

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Abstract. – *Background:* **The purpose of this study was to evaluate the ability of rectal suppository of hyaluronic acid to limit symptoms of acute radiation proctitis in patients with prostate cancer (PC).**

Materials and Methods: **From January 2011 to October 2011, 50 consecutive patients, undergoing radiotherapy with radical or adjuvant intent for PC, were invited to use rectal suppository of hyaluronic acid (HA: Cicatridina® suppository, Farma-Derma s.r.l., Sala Bolognese, BO, Italy) daily, before radiation delivering. An historical group was used as an external control. Acute rectal toxicity was scored weekly according to RTOG criteria. Time to occurrence of acute rectal toxicity was taken as endpoint.**

Results: **Compliance was good. Only 2% of HA treated patients had a G2 acute proctitis versus 7% of historical group, globally a difference was observed in rate of acute proctitis between the experimental arm and the control group: 32% in experimental arm versus 45% in control group ($p = 0.08$). A delay in the onset of acute rectal toxicity in patients treated with HA ($p = 0.04$) was showed.**

Conclusions: **Our findings suggested the role of HA in reducing acute proctitis in prostate cancer patients treated with radiotherapy. Further trials are needed to confirm these results.**

Key Words:

Acute proctitis, Radiotherapy prophylaxis, Hyaluronic acid.

Background

Prostate cancer (PC) is the second most frequently diagnosed cancer among men and the sixth leading cause of cancer death in men worldwide. From the available global statistics, in 2007, an estimated 782,600 new cases were diagnosed and 254,000 patients died of PC[1]. Definitive external-beam radiotherapy (EBRT) represents an important treatment modality with curative intent for men with localized PC. Several randomized trials have shown that escalation of radiation dose improves outcomes in prostate cancer patients[2-4]. However, when a high dose is delivered, is likely that rectum toxicity increases. Indeed, rectal injury is a dose-limiting toxicity of radiotherapy for prostate cancer, it produces patient discomfort and reduces both patient compliance to treatment and quality of live[5]. Many pharmacological agents have been used with prophylactic treatment for radiation rectal injuries: sucralfate[6-9], 5-aminosalicylic acid (5-ASA) and its precursors[6,10-12], corticosteroids[13,14]; some studies showing a reduction of rectal toxicity, but with others showing no effect or possibly worsening of symptoms[9]. Hyaluronic acid (HA), a major mucopolysaccharide, is clinically used in prevention of radiation cystitis[15] and skin reaction[16]. A recent study demonstrated a radioprotective effect of HA acid in intestinal mucosa[17]. HA reduces radiation induced apoptosis and increases crypt survival. However, no clinical trials have investigated the role of this mucopolysaccharide in the prevention of acute proctitis in prostate cancer during radiotherapy. The development of a non-toxic agent, that could simply be administered during radiotherapy to prevent toxicity, would be an important therapeutic advance in prostate cancer. In order to clarify this issue, we decided to analyze whether HA have any role in preventing acute proctitis due to radiotherapy.

Materials and Methods

Patients and Treatment

Men referred for pelvic radiotherapy for prostate cancer, as adjuvant or radical treatment, were con-

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sidered for this study. The eligibility criteria included: signed informed patient consent; age less than 80 years; Karnofsky PS (Performance status) ≥ 60; treatment with radiation doses more than 65 Gy. Patients were ineligible if they had had more than two open pelvic or abdominal surgical procedures; if they had diabetes mellitus, inflammatory bowel disease, active intraluminal gastrointestinal tumors, or a previous history of pelvic RT. Adjuvant hormonal therapy was permitted. The ACE-27 was used to take into account co-morbidities[19] prospectively for experimental arm and retrospectively for historical control. In the presence of more than one co-morbidity related to an organ system the one with the highest severity was counted. The patients were divided in four subgroups: "no", "mild", "moderate" and "severe" co-morbidities. To test hypothesis that HA could be effective in preventing acute radiation proctitis, in these patients, rectal suppository of hyaluronic acid (Cicatridina® suppository, Farma-Derma s.r.l., Sala Bolognese, BO, Italy) was daily used concomitantly with radiation delivery. We evaluated 50 consecutive patients: 19 received radiotherapy as adjuvant therapy, instead 31 with a radical intent. Due to the lack of both financial support and drug company interest, we did not have the possibility to provide patients with a placebo product manufactured in the same way as the medical device. In order to obtain a baseline level of proctitis for our center, we have used an historical control group received a radiotherapy program from January 2007 to March 2008, 38 patients treated postoperatively and 62 radically. The patient groups were comparable in terms of patient characteristics, radiation dose (total dose and fractionation dose) and radiation technique. This is a case-versus historical control study. To obtain homogeneous data on toxicity, acute morbidity was classified according to the Radiation Therapy Oncology Group (RTOG) criteria (Table I)[18] and recorded weekly during radiation.

Radiation Treatment

All patients, experimental group and historical control, had conformal radiotherapy with 15 MV photon beams using CT-assisted three-dimensional treatment planning (Pinnacle3 Philips Healthcare P.O. Box10.000 5680DA Best TheNetherlands). When a radical radiation treatment was delivered, patients received a median prescription dose of 60 Gy (50-66 Gy) in 2 Gy fractions to the prostate and seminal vesicles plus a 1 cm margin, except posteriorly where the margin was 0.5 cm. Then patients underwent a treatment to the prostate alone using a shrinking field technique with a 1 cm margin to a median prescription dose of 18 Gy (12-28 Gy) in 2.0 Gy fractions. Instead, in adjuvant setting, patients received 70 Gy in 2.0 Gy fractions to the surgical bed plus a 1 cm margin, except posteriorly where the margin was 0.5 cm. Dose was prescribed according to the ICRU 50 (International Commission on Radiation Units & Measurements, 1993) guidelines. All treated patients, in experimental and historical control arm, had a low probability of toxicity, defined as a dose-volume histogram (DVH) below the reference DVH curve defined by the following points: V40 = 60%, V50 = 50%, V60 = 28%, V72 = 15%, V76 = 5%, where VX (%) is the percentage of volume receiving an X (Gy) dose[5].

All patients were treated with radiotherapy image guided, acquiring 3D image weekly and two 2 D images daily.

Patient Evaluations

According to our policy, we evaluated PC patients during radiotherapy weekly and scored according RTOG toxicity criteria for each of the following toxicities: proctitis, diarrhea, dysuria, fatigue, weight loss, nausea, and vomiting. Actual patient weight was also recorded at each evalu-

Table I. Acute proctitis according to RTOG scoring system[3]. GI: gastrointestinal.

Grade				
0	1	2	3	4
No change	Increased frequency or change in quality of bowel habits not requiring medication; rectal discomfort not requiring analgesics	Diarrhea requiring parasympatolytic drugs/ mucus discharge not necessitating sanitary pads; rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support; severe mucus or blood discharge necessitating sanitary pads; abdominal distension	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

ation. In experimental group, it was allowed to treat symptomatic patients with the same modalities than historical control in addition to suppository of hyaluronic acid. Evaluations continued throughout RT and concluded with a 4-week post treatment visit. Historical control group included prostate cancer patients consecutively treated in our Radiation Department from 2007 to 2008 with definitive or adjuvant radiotherapy. Data were extrapolated from single case history.

Statistical Analysis

The primary endpoint of the study was the time to occurrence of acute rectal toxicity. Symptom data were analysed by one way analysis of variance and paired t-tests were used for estimating group differences between experimental arm and historical control arm. Survival curves were calculated using the Kaplan-Meier method from the date of treatment start. Differences in acute toxicity rate were assessed by the log-rank test. Actuarial incidence of acute reactions was analyzed in relation to clinical variables: age, comorbidity, performance status and radiation dose, using univariate and multivariate analyses.

All analyses were conducted with SPSS vers.13.0 (SPSS for Windows, Rel. 13.0 2004. SPSS Inc., Chicago, IL, USA).

Results

Features of Patients at Baseline

All patients in experimental group were eligible for the analysis. Ten out of 50 patients (20%) were over 75 years old, 30 (60%) ranged between 70-74 years and 10 (20%) between 65-69 years. In this cohort, 19 patients (38%) received a postoperative radiotherapy treatment with a dose ≥ 66 Gy with conventional fractionation and 31 patients (52%) received a radical radiotherapy with a dose ≥ 74 Gy.

Twenty-four (48%), 15 (30%) and 11 (22%) patients had a Gleason score of ≤ 6, 7 and > 7, respectively. In 37 (74%) patients was observed at least one co-morbidity. The patients' classification of co-morbidities according to adult comorbidity evaluation-27 (ACE-27) index was 0 in 13 (26%) patients, 1 in 27 (54%), 2 in 9 (18%) and 3 in 1 (2%) patients, respectively. The Karnofsky PS score was: 60, 70-80 and ≥ 90 in 4 (8%), 26 (52%) and 20 (40%) patients, respectively. Twenty-six patients (52%) received radiotherapy in combination with 6 months of androgen suppression therapy. All patients completed the planned treatment. As historical control group, we analyzed retrospectively 100 prostate cancer patients treated in our Radiotherapy Department from 2007 to 2008, 62 patients (62%) treated radically and 38 (38%) postoperatively. Patient and treatment characteristics of experimental and historical control group are shown in the Table II. Seventeen out of 100 patients (17%) were over 75 years old, 69 (69%) ranged between 70-74 years and 14 (14%) between 65-69 years. The patients' classification of co-morbidities according to ACE-27 index was 0 in 28 (28%) patients, 1 in 52 (52%), 16 in 2 (16%) and 4 in 3 (4%) patients, respectively. The Karnofsky PS score was: 60, 70-80 and ≥ 90 in 9 (9%), 54 (54%) and 37 (37%) patients, respectively.

Evaluation of Acute Toxicity

Compliance was good, with only one patient not completing the assigned rectal suppository of hyaluronic acid for an acute anal fissure. In experimental group, only 16 patients (32%) developed acute rectal toxicity, 14 of them (28%) reported increased frequency and rectal discomfort not requiring analgesics, therefore, a rectal toxicity classified as G1. Only a patient reported a G2 toxicity. None of the patients developed grade 3 or 4 acute reactions. In historical control group, 45 patients (45%) developed radiation toxicity, 38 patients a G1 rectal toxicity and 7 a G2 toxicity. No significant difference ($p = 0.21$) was observed between experimental and historical group (Figure 1).

The acute toxicity-free rate at the end of treatment was 68% ± 6% in HA arm and 55 % ± 5% in historical control group ($p = 0.04$) (Figure 2). In arm treated with suppository of hyaluronic acid, radiation proctitis was recorded before 5 weeks in only 10% of patients.

The results of the univariate analysis are shown in the Table III, no variable showed predictive value.

Discussion

Acute radiation proctitis is the most relevant acute side effect following external beam irradiation for prostate cancer. In literature, it occurrs in up to 75% of patients[20-22] and results in bleeding, pain, abdominal cramping, mucoid discharge, and faecal urgency. The onset of symptoms reduces patient compliance, therefore, also radiation efficacy. Consequently, an agent, administered during radiotherapy to prevent toxicity, would be an important therapeutic advance in prostate cancer.

Table II. Clinical characteristics of the patients

Parameters	Experimental group N (%) HA suppository	Historical group N (%)
Age (years)		
Range	66-80	67-82
Mean	72.06	72.20
Age-groups		
65-69	10 (20%)	14 (14%)
70-74	30 (60%)	69 (69%)
> 74 years	10 (20%)	17 (17%)
ACE-27 overall comorbidity score		
Grade 0	13 (26%)	28 (28%)
Grade 1	27 (54%)	52 (52%)
Grade 2	9 (18%)	16 (16%)
Grade 3	1 (2%)	4 (4%)
PS		
90-100	20 (40%)	37 (37%)
70-80	26 (52%)	54 (54%)
60	4 (40%)	9 (9%)
PSA (ng/ml)		
< 10	19 (38%)	39 (39%)
10-20	22 (44%)	42 (42%)
> 20	9 (18%)	19 (19%)
Gleasone score		
≤ 6	24 (48%)	50 (50%)
7	15 (30%)	32 (32%)
> 7	11 (22%)	18 (18%)
Radiotherapy		
Adjuvant	19 (38%)	38 (38%)
Radical	31 (62%)	62 (62%)
Hormonal therapy		
Yes	24 (48%)	51 (51%)
No	26 (52%)	49 (49%)

Table III. Univariate analysis of survival data according to various classifications.

Parameters	Groups	β	± S.E.M.	*p* =	HR (95% CI)
Age category	0: 65-69 1: 70-84 2: > 75	-0.088	0.197	0.654	0.916 (0.623-1.346)
Comorbidity	0: none 1: mild 2: moderate 3: severe	0.122	0.153	0.425	1.130 (0.837-1.524)
PS	0: 90-100 1: 70-80 2: 60	-0.018	0.207	0.931	0.982 (0.655-1.473)
PSA (ng/ml)	0: < 10 1: 10-20 2 > 20	-0.144	0.179	0.421	0.866 (0.610-1.229)
Gleason score	0: ≤ 6 1: 7 2: ≥ 7	-0.110	0.168	0.515	0.896 (0.645-1.246)
Radiotherapy	0: aduvant 1: radical	0.450	0.281	0.109	1.568 (0.904-2.719)

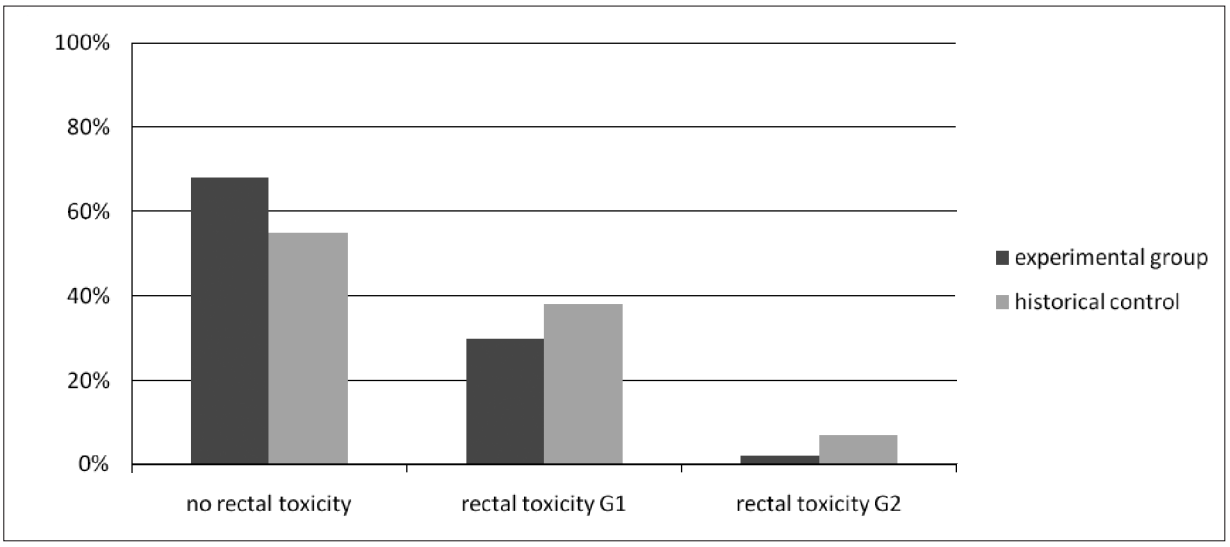

Figure 1. Distribution of no rectal toxicity and of G1 and G2 toxicity for all patients.

Since there are conflicting results in trials available comparing the existing treatment options, firm guidelines cannot be made. Attempts to reduce radiation-induced proctitis using various agents such as steroids, mesalazine, sucralfate and other have not met with success, probably for multi-factorial genesis of radiation proctitis.

Withers and Mason, in 1974, first identified crypt depletion and deep inflammatory infiltrate in the colon mucosa as a major effect of radiation[23]. Disepithelization of the gut mucosa allows intestinal contents, e.g., microorganisms, foreign antigens, and proteolytic enzymes, access to stromal tissue compartments. This elicits inflammatory and fibrogenic responses that may further damage the mucosa and possibly set the stage for chronic changes in the deep layers of the bowel wall[24]. Hyaluronic acid is a major mucopolysaccharide

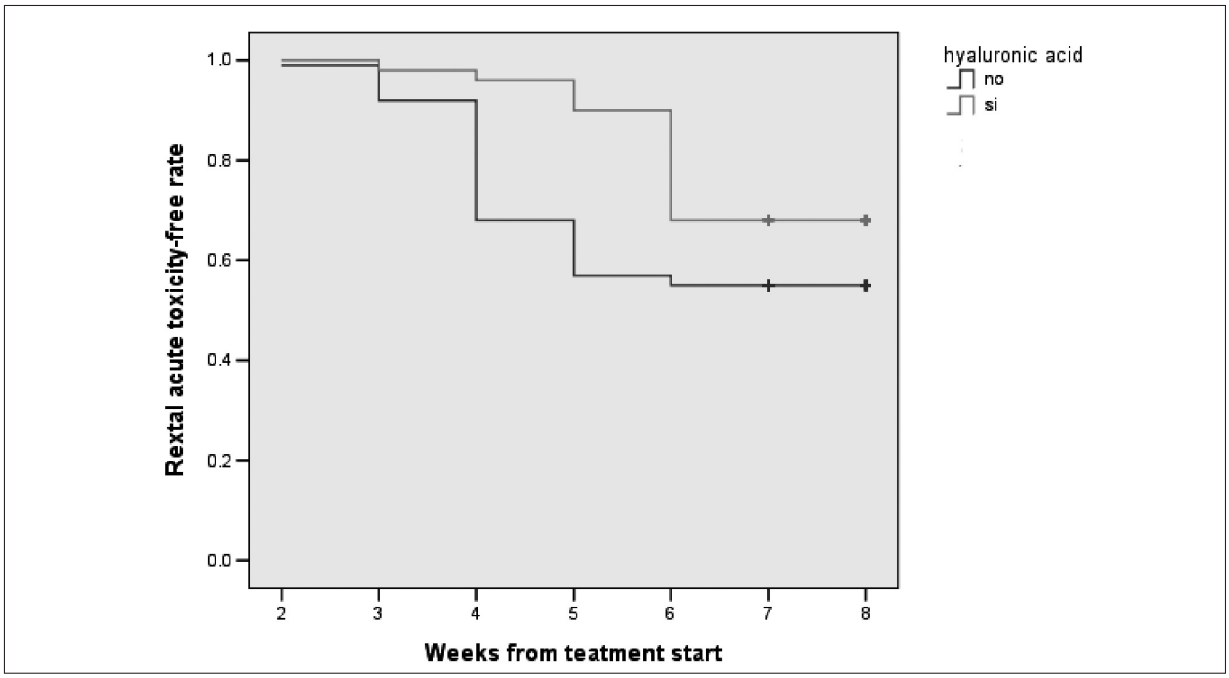

Figure 2. Time to occurrence of acute rectal toxicity for all patients evaluated: 50 treated with HA rectal suppository and 100 historical control.

found widely in the connective, epithelial and neural tissues. It exhibits a variety of properties that could explain a prophylactic mechanism of pathogenesis of radiation proctitis: inhibition of immune complexes, adherence to polymorphonuclear cells, inhibition of leucocyte migration, regulation of fibroblast and endothelial cell proliferation, enhancement of connective tissue healing, etc[25]. A recent study[17] showed that hyaluronic acid, in animal model, reduces radiation apoptosis and increases intestinal crypt survival. Riehl et al[17] clearly demonstrated that HA, administering before radiotherapy, could prevent radiation injury through a bond with tool-like receptor 4 (TLR 4) and an increase in expression of cyclo-oxygenase-2 (COX-2) and prostaglandin E2 (PGE2). This appealing theory could explain molecular mechanism under protection of radiation injury in humans too. Nevertheless, HA is clinically used to treat radiation cystitis[15] and other radiation injuries[16,26] with beneficial results. The aim of the present study was to analyze whether HA has any role in preventing acute proctitis due to radiotherapy in prostate cancer patient. HA is topically administered by suppository to protect rectal mucosa normally irradiated only for geometrically and dosimetric reasons.

We did not have the possibility to provide patients with a placebo product manufactured in the same way, so we did not have possibility to test HA in a double-blind randomized study. Therefore, we decided to use an external control consisting of patients treated at an earlier time in our Radiotherapy Department. This historical control group has characteristics very similar to patient group treated with HA and have been treated in a similar setting (adjuvant and radical radiotherapy) and in a similar manner (same dose, fractionation and machines). Furthermore, the rate of acute proctitis after radiotherapy, to treat prostate cancer, is well known and vary little in literature. In this study, the rate of acute proctitis is 40.7%, with a G2 rate of 5%, these values are comparable with literature data using image guided radiotherapy and same dose of radiotherapy[27].

In our analysis, rectal suppository of hyaluronic acid administered before radiation is well tolerated, only one patient discontinued treatment. Globally, a difference was observed in rate of acute proctitis between the experimental arm and the control group: 32% in experimental arm versus 45% in control group, although only 2% of HA treated patients had a G2 acute proctitis versus 7% of historical group. Furthermore, analysis of time to occurrence of acute rectal toxicity shows a delay in the onset of symptoms in patients treated with HA ($p = 0.04$). This effect could be used to increase compliance of prostate cancer patients to radiation therapy. The use of image guided radiotherapy, reducing inadvertent dose deposition in the adjacent rectal tissues[28], decreases the rate of acute proctitis. However, in most radiotherapy department image guided radiation therapy is not standard treatment, therefore, rectal toxicity has a rate higher than observed in this study. So, improved results could be expected from HA rectal suppositories to prevent acute radiation induced proctitis.

In conclusion, our findings suggested the role of HA in reducing acute proctitis in prostate cancer patients treated with radiotherapy. It's important validate these results with other clinical trials.

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