Clin Transl Oncol (2009) 11:828-834
DOI 10.1007/s12094-009-0451-6

RESEARCH ARTICLES

Vesical instillations of hyaluronic acid to reduce the acute vesical toxicity caused by high-dose brachytherapy do not affect the survival: a five-year follow-up study

Pilar M.ª Samper Ots · Concha López Carrizosa · Aurora Rodríguez · Juan de Dios Sáez · José María Delgado · Manuel Martín de Miguel · Montserrat Vidal

Received: 19 May 2009 / Accepted: 14 September 2009

Abstract
Objective To determine whether the intravesical use of hyaluronic acid (HA) reduces acute and late vesical toxicity induced by radiotherapy.
Methods Single-centre retrospective study of patients diagnosed with cervical and endometrial cancer treated with brachytherapy (BT) with or without intravesical instillation of HA. Patients were assigned consecutively to the two treatment groups. Forty milligrams of HA was instilled intravesically for approximately 30 min prior to each BT session. Rates of acute and late vesical toxicity were recorded using the RTOG criteria.
Results Ninety-five clinical histories were reviewed (48 with HA instillation and 47 without). Surgery had been performed in 85.3% of cases, external radiotherapy in 76.8% and chemotherapy in 25.3%. There were no significant differences between groups with regard to the total number of BT sessions, dose per session, total dose or biological equivalent dose. In all the sessions the percentage of patients presenting acute vesical toxicity was lower in the HA group, the differences being statistically significant ($p<0.05$) after the 2nd (20.8% vs. 40.4%) and 4th sessions (10.9% vs. 31.9%). No patients in the HA group presented vesical toxicity after six months of follow-up. Over the whole study period, the percentage of patients presenting vesical toxicity of degree 2 or more was significantly lower in the HA group (2.08% vs. 12.8%; $p<0.05$).
Conclusion Vesical instillations of HA decrease the incidence and the degree of acute vesical toxicity induced by high-dose BT, and reduce the percentage of patients that develop toxicity of degree 2 or more.

Keywords Brachytherapy · Hyaluronic acid · Vesical toxicity

Introduction

Acute bladder toxicity is a frequent complication of radiotherapy for pelvic tumours. During irradiation, the proliferative activity of the endothelium is reduced; this causes acute cystitis, which presents as dysuria, pollakiuria and urinary urgency. The subsequent vascular occlusion and focal ischaemia are responsible for late bladder toxicity [1].

The glycosaminoglycan (GAG) layer of the luminal surface of the bladder constitutes an aqueous barrier between the urothelial surface and the bladder's contents. GAGs act as a defensive barrier against pathogens, microcrystals and other elements present in the urine [2]. GAG deficiency may be one of the causes of cystitis of unknown aetiology, whose pathological changes are very similar to those of radio-induced cystitis.

Hyaluronic acid (HA) is a linear, non-sulphated, non-protein-binding GAG that consists of a repetition of disaccharide units formed by D-glucuronic acid and N-acetyl glucosamine. It forms part of the GAG layer protecting the

P.M.ª Samper Ots (✉) · C. López Carrizosa · A. Rodríguez · J. de Dios Sáez · J.M. Delgado · M. Martín de Miguel
Servicio de Oncología Radioterápica
Hospital Central de la Defensa Gómez Ulla
C/ Glorieta del Ejército, s/n
ES-28047 Madrid, Spain
e-mail: psamots@oc.mde.es

M. Vidal
Clever Instruments, S.L.
Barcelona, Spain

Table 1 Patients and tumour characteristics

Age (years)	HA group	non-HA group	*p**
(mean [CI 95%])	63.6 [59.8–67.4]	62.4 [58.8–67.0]	0.651
Type of tumour	N (%)	N (%)	*p***
Localisation			
Cervical cancer	11 (22.9)	16 (34.0)	0.318
Endometrial cancer	36 (75.0)	31 (66.0)	
Vaginal cancer	1 (2.1)	–	
Histology			
Adenocarcinoma	37 (77.1)	31 (66.0)	
Epidermoid cancer	10 (20.8)	16 (34.0)	0.234
Sarcoma	1 (2.1)	–	
FIGO stage			
Stage I	23 (47.9)	20 (42.6)	0.804
Stage II	10 (20.8)	15 (31.9)	
Stage III	12 (25.0)	9 (19.1)	
Stage IV	2 (4.2)	2 (4.3)	
Recurrence	1 (2.1)	1 (2.1)	
Histological grade			
G1	19 (40.4)	18 (42.9)	0.271
G2	14 (29.8)	12 (28.6)	
G3	12 (25.5)	6 (14.3)	
Gx	2 (4.3)	6 (14.6)	

**p*-value obtained by one-way analysis of variance (ANOVA)
***p*-value obtained by Chi squared test

apical zone of the bladder epithelium, which blocks the passage of substances and germs, thanks to its hydrophilic properties and its high negative charge [3].

Since 1995, intravesical instillations of HA have been used to treat refractory interstitial cystitis [4]. The absorption of HA is minimal; after instillation, high concentrations are reached in direct contact with the vesical mucosa, which makes it an effective treatment [5]. What is more, the fact that it is a natural component of the extracellular matrix means that it does not produce allergic reactions and is therefore safe to use. In a study conducted at our Radiotherapy Oncology Service in 2001, we showed that weekly intravesical administration of HA in patients receiving radiotherapy for gynaecological tumours had a protective effect against bladder toxicity [6].

In our daily clinical practice we routinely use HA, in suppositories or vaginal ovules, for the prevention and treatment of acute and late radio-induced rectitis and vaginitis in patients undergoing pelvic radiotherapy. The results obtained have been excellent. Since September 2002, patients with gynaecological tumours receiving brachytherapy (BT) as part of their routine treatment have been randomly administered intravesical HA according to the type of tumour.

The present study aims to determine whether intravesical instillations of HA can prevent acute and late radio-induced cystitis. Little information is currently available on the use of HA in radiotherapy for prevention of radio-induced toxicity. Here we present the results obtained in our series to date.

Material and methods

Patients and treatment

After approval by the Ethics Committee of our hospital, we reviewed the clinical histories of 95 patients with gynaecological tumours (27 cervical, 67 endometrial and one vaginal cancers) treated at the Radiotherapy Oncology Service at the Hospital Central de la Defensa in Madrid, between September 2002 and June 2007. The mean age was 62.9±12.6 years (range 36–88 years). The characteristics of patients and tumours are shown in Table 1.

All patients received routine treatment for their tumour type and stage, in accordance with the service's standardised protocols.

Eighty-one patients (85.2%) underwent surgery. In 73 patients (76.8%) external three-dimensional conformal radiotherapy (3DCRT) was delivered. Total pelvic dose was 46–50 Gy, delivered in 23–25 fractions of 2 Gy (46 Gy in 49 patients (67.1%) and 50 Gy in 6 (8.2%)). In 18 patients (24.7%) a parametrial boost was delivered up to 56 Gy. The mean bladder dose was 45.2±3.5 Gy (range 35.8–54.5 Gy) to 87.1±7.3% (range 61–97%). Twenty-four patients (25.2%) underwent chemotherapy.

All cases received intracavitary high-dose-rate BT either alone (23.2%) or in addition to 3DCRT (76.8%). BT was performed weekly. In the patients who received BT and 3DCRT, BT was also performed weekly, alternately with 3DCRT. No external radiation was delivered the same day of the implant.

Table 2 Characteristics of cancer treatment

Treatment	HA group N (%)	Non-HA group N (%)	*p**
Surgery	42 (87.5)	39 (83.0)	0.575
HT+DA	10 (20.8)	10 (21.3)	
HT+DA+LD	9 (18.8)	5 (10.6)	
Wertheim-Meigs hysterectomy	20 (41.7)	21 (44.7)	
Other	3 (6.3)	3 (6.4)	0.787
External radiotherapy	35 (72.9)	38 (80.9)	0.467
Chemotherapy	10 (20.8)	14 (29.8)	0.352
Applicator BT			
One channel cylindrical	42 (51.9)	39 (48.1)	
One intrauterine tube and two vaginal ovoid	6 (42.9)	8 (57.1)	0.37
	Mean [CI 95%]	Mean [CI 95%]	**
Total dose 3DCRT (Gy)	48.35 [46.96–49.7]	49.21 [47.7–50.6]	0.398
Mean bladder dose 3DCRT (Gy)	44.6 [43.4–45.9]	45.7 [44.5–46.9]	0.213
% bladder underwent mean dose	87.3 [84.7–90.09]	86.8 [83.3–89.2]	0.753
BT			
Total number of implants	5.0 [4.74–5.36]	4.9 [4.70–5.13]	0.617
Dose per implant (cGy)	478.1 [457.6–498.6]	505.3 [480.0–530.6]	0.095
Total dose BT (Gy)	24.0 [22.14–25.91]	24.9 [23.12–26.60]	0.511
Biological equivalent dose BT (Gy)	35.6 [32.21–38.97]	37.8 [34.46–41.18]	0.349
Maximal bladder dose BT (Gy)	21.8 [19.23–24.51]	21.14 [19.08–23.16]	0.663

**p*-value obtained by Fisher's exact test

***p*-value obtained by one-way analysis of variance (ANOVA)

HT, total hysterectomy; *DA,* bilateral adnexectomy; *LD*, lymphadenectomy

The BT applicator was a vaginal cylinder in 81 patients (85.3%) and a uterine tandem with two vaginal colpostats in 14 (14.7%). The mean total numbers of implants was 4.96±0.82 (range 3–7), the mean dose per implant was 491.58±79.44 cGy (range 400–650 cGy), the mean dose total of BT was 24.4±6.19 Gy (range 15–42 Gy) and the mean biological equivalent dose was 36.69±11.53 Gy (range 21.7–70 Gy). The total maximal bladder dose of BT was 21.51±8.09 Gy (range 8.57–51.22 Gy) and was significantly higher when the applicator was a uterine tandem with two vaginal colpostats 27.99±9.71 Gy rather than a vaginal cylinder 20.39±7.28 Gy (p=0.001).

We calculated the maximum bladder dose in each application of BT and the accumulated maximum dose.

According to the type of tumour, the patients were consecutively assigned to receive HA (HA group) or not (non-HA group). The treatment with HA (Cystistat®, Bioniche Pharma; distributed in Spain by Laboratorios Rubió, S.A.) comprised intravesical instillation of 50 ml of sterile solution with 40 mg of the molecule prior to each BT insertion, when the routine catheterisation was performed to calculate the dose delivered to the bladder. The HA was maintained for approximately 30 min inside the vesical cavity while the BT was prepared.

The HA group includes 48 women and there were 47 in the non-HA group. The characteristics of cancer treatment in each group are shown in Table 2; there were no statistically significant differences between groups that were submitted to surgery, radiotherapy, total dose 3DCRT, mean bladder dose 3DCRT, percentage of bladder that received the mean bladder dose, chemotherapy, BT applicator, total number of implants, dose per implant, total dose BT, biological equivalent dose BT and maximum bladder dose BT.

Follow-up

Before the start of the study, and before each weekly BT session, acute bladder toxicity was evaluated using the RTOG/EORTC acute toxicity criteria. After the end of treatment periodical follow-up was performed, for five years, in which bladder toxicity was evaluated according to the RTOG/EORTC late toxicity criteria at 3, 6, 12, 18, 24, 30, 36, 48 and 60 months [7].

Statistical analysis

The data from the clinical histories were analysed using the SPSS for Windows statistical package (version 13.0). The homogeneity of the two groups with regard to BT and 3DCRT was checked by comparing the total number of implants, doses per application, total dose BT, equivalent biological dose BT, maximum bladder dose BT, total dose 3DCRT and mean bladder dose 3DCRT recorded in the clinical histories (one-factor ANOVA and Mann–Whitney tests). We also checked that there were no significant differences in terms of the percentage of patients undergoing surgery, 3DCRT and chemotherapy by means of between-groups comparison (Chi squared test).

Table 3 Radiation toxicity grade during treatment and follow-up

Toxicity grade Treatment	HA group				Non-HA group				*p*-value*
	0	1	2	3	0	1	2	3	
Baseline	48 (100%)				45 (95.7%)	2 (4.3%)			0.151
1st HDR	44 (91.7%)	4 (8.3%)			38 (80.9%)	8 (17.0%)	1 (2.1%)		0.121
2nd HDR	38 (79.2%)	9 (18.8%)	1 (2.1%)		28 (59.6%)	18 (38.3%)	1 (2.1%)		<0.05
3rd HDR	40 (83.3%)	7 (14.6%)	1 (2.1%)		32 (68.1%)	12 (25.5%)	2 (4.3%)	1 (2.1%)	0.077
4th HDR	41 (89.1%)	4 (8.7%)	1 (2.2%)		32 (68.1%)	14 (29.8%)	1 (2.1%)		<0.05
5th HDR	29 (85.3%)	5 (14.7%)			22 (66.7%)	9 (27.3%)	2 (6.1%)		0.064
6th HDR	14 (100%)				8 (72.7%)	3 (27.3%)			<0.05
Follow-up									
Month 3	41 (91.1%)	4 (8.9%)			34 (81.0%)	6 (14.3%)	2 (4.8%)		0.156
Month 6	37 (92.5%)	3 (7.5%)			32 (86.5%)	3 (8.1%)	2 (5.4%)		0.360
Month 12	33 (100%)				26 (89.7%)	1 (3.4%)	2 (6.9%)		0.060
Month 18	28 (100%)				21 (91.3%)		2 (8.7%)		0.115
Month 24	23 (100%)				17 (89.5%)	1 (5.3%)	1 (5.3%)		0.115
Month 30	21 (100%)				17 (94.4%)		1 (5.6%)		0.280
Month 36	17 (100%)				13 (92.9%)	1 (7.1%)			0.270
Month 48	13 (100%)				8 (88.9%)	1 (11.1%)			0.229
Month 60	4 (100%)				2 (66.7%)	1 (33.3%)			0.248

*p-value obtained by Mann–Whitney U-test

The rate of acute and late bladder toxicity was studied on the basis of the variables p*resence or absence of bladder toxicity* at each of the control visits. To assess the gravity of the toxicity, the variables toxicity *grade 2 or above* were created for each control session: *acute toxicity grade 2 or above* (appearance of toxicity grade 2 or above in one or more of the controls during the therapy phase), *late toxicity grade 2 or above* (appearance of toxicity grade 2 or above in one or more of the controls during the post-radiotherapy follow-up) *and overall toxicity grade 2 or above* (appearance of toxicity grade 2 or above in one or more of the controls within 60 months of the start of the BT).

The effect of HA vesical instillation on the appearance and gravity of acute and late radio-induced bladder toxicity was studied by comparing the rates of toxicity and toxicity grade 2 or above at each control session in the two treatment groups. We used univariate Chi squared tests to compare proportions (or the Fisher's exact test when the sample size was below 20). We also compared confidence intervals and calculated relative risk or odds ratios (OR).

We investigated the relationship between the main features of the tumour and treatment variables (tumour type, FIGO stage, 3DCRT, chemotherapy and total BT dose) and the incidence and gravity of acute and late bladder toxicity. We used univariate tests to compare proportions in the case of dichotomous variables (Chi squared test or Fisher's exact test and calculation of the relative risk or OR) or to compare means in the case of numerical variables (one-way ANOVA and Mann–Whitney U non-parametric tests).

In the main cases in which univariate tests showed significant differences in toxicity between the two groups, we performed multivariate tests with logistic regression models to confirm the incidence of different variables as independent factors able to influence the appearance and gravity of radio-induced bladder toxicity.

To rule out the possible influence of the use of intravesical instillations of HA on patient survival, we generated disease-free and overall survival curves using the Kaplan–Meier method, and studied the possible differences between groups using the Log-Rank statistic.

The level of significance was set at $p<0.05$ for all the tests.

Results

Acute bladder toxicity

The acute bladder toxicity during BT in each group was shown in Table 3. Only one patient non-HA group had toxicity grade 3. The percentages of patients presenting acute bladder toxicity did not present significant differences between groups (HA: 41.7% vs. non-HA: 55.3%; n.s.). Nonetheless, throughout the treatment, the weekly rates tended to be lower in the HA group and were significantly lower after the second session (HA: 20.8% vs. non-HA: 40.4%; OR: 2.58 [95% CI: 1.04–6.4]; $p<0.05$) and the fourth session (HA: 10.9% vs. non-HA: 31.9%; OR: 3.84 [95% CI: 1.3–11.7]; $p<0.05$) (Fig. 1).

These results were confirmed by the multivariate analysis controlling for tumour type, FIGO stage, 3DCRT, chemotherapy and total BT dose. The relationship between instillation of HA and appearance or non-appearance of toxicity increased after the second session, reaching an OR: 3.82 [95% CI: 1.38-10.64]; $p<0.01$), and after the fourth session, with an OR: 5.21 [95% CI: 1.56–17.24]; $p<0.01$).

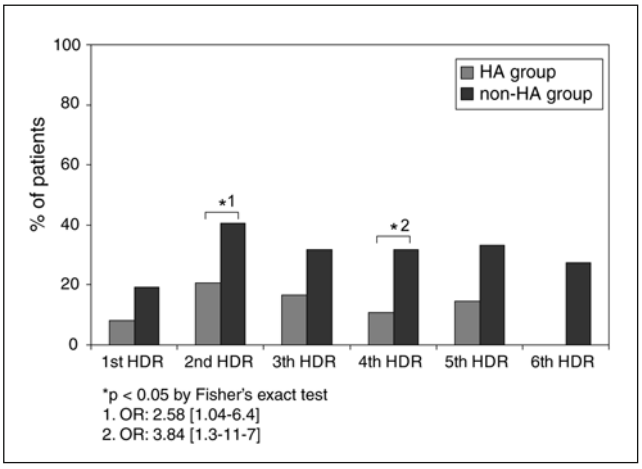

Fig. 1 Percentage of patients presenting acute vesical toxicity before each high-dose-rate BT (HDR)

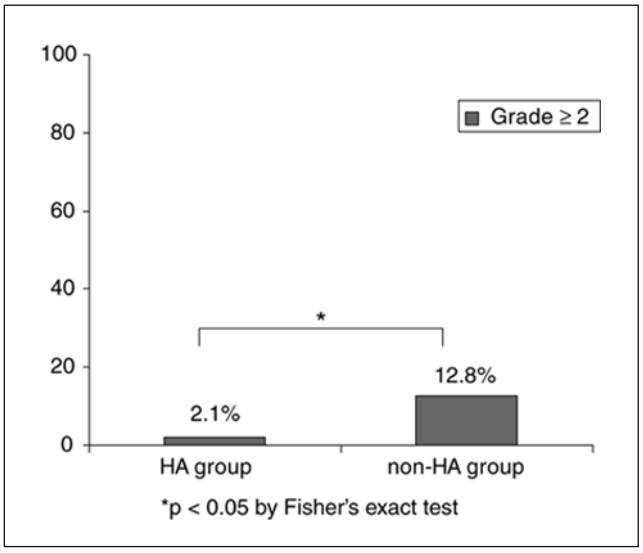

Fig. 2 Percentage of patients presenting vesical toxicity grade of 2 or more

3DCRT also showed a significant relationship with the increase in the rate of toxicity after the third session (30.1% vs. 4.5%; OR: 9.09 [95% CI: 1.15–71.43]; $p<0.01$). This relationship remained significant, though less powerful (OR: 8.62 [95% CI: 1.08–68.75]; $p<0.05$) after controlling for the effect of HA in the multivariate tests. There was no significant relationship between total dose 3DCRT, mean bladder dose 3DCRT and degree acute bladder toxicity.

There were no significant relationships between accumulated maximum bladder doses BT and weekly acute bladder toxicity in the total group and in each group (Table 4).

There was no significant relation between BT applicator and weekly acute bladder toxicity, probably because only 14 patients were treated with an intrauterine tandem and two vaginal colpostats vs. a vaginal cylinder in 81 patients.

Late toxicity

The late bladder toxicity during follow-up in each group is shown in Table 3. A relation was established between mean bladder dose 3DCRT, percentage that received the mean bladder dose, maximum bladder dose BT and late bladder toxicity. The rate of late toxicity at the first 3 and 6 months post-treatment was 8.9% and 7.5% in the HA group compared with 19.0% and 13.5% in the non-HA group. Though no significant differences were found between the treatment groups, from 6 months and until the end of follow-up, no patient in the HA group presented bladder toxicity,

Table 4 Relationship between acute bladder toxicity grade and accumulated maximum bladder doses BT

HDR	Grade toxicity	Total			HA group			Non-HA group		
		N	Mean	*p*	N	Mean	*p*	N	Mean	*p*
1st HDR, N=95	0	82	446.9		44	441.0		38	453.6	
	1	12	331.7		4	353.7		8	320.7	
	2	1	348.0	0.046	–	–	0.371	1	348.0	0.010
2nd HDR, N=95	0	66	888.1		38	865.2		28	919.1	
	1	27	774.9		9	785.6		18	769.6	
	2	2	784.3	0.163	1	950.6	0.735	1	618.0	0.057
3rd HDR, N=95	0	72	1313.9		40	1275.8		32	1361.5	
	1	19	1198.0		7	1241.7		12	1172.5	
	2	3	1162.5		1	1425.9		2	1030.8	
	3	1	1073.0	0.602	–	–	0.924	1	1073.0	0.264
4th HDR, N=93	0	73	1738.1		41	1742.7		32	1732.3	
	1	18	1694.6		4	1467.2		14	1759.6	
	2	2	1654.1	0.937	1	1901.2	0.661	1	1407.0	0.780
5th HDR, N=66	0	50	2146.1		29	2174.3		21	2107.0	
	1	14	2217.3		5	1859.0		9	2416.5	
	2	2	1762.0	0.719	–	–	0.446	2	1762.0	0.292
6th HDR, N=23	0	20	2881.4		14	2931.5		6	2764.4	
	1	3	3076.6	0.625	–	–	–	3	3076.6	0.562

compared with 3 patients in the non-HA group. None of the other factors studied showed a significant relationship with the rate of late toxicity in any of the control sessions.

Grade of toxicity

The maximum grade of acute toxicity in the HA group was grade 2 (found in only one patient). In the non-HA group, four patients presented toxicity grade 2 and one patient toxicity grade 3. The maximum grade of late toxicity in the HA group was grade 1 and in the non-HA group grade 2 (see Table 3). There were no significant differences between groups with respect to the percentage of cases of acute toxicity or late toxicity grade 2 or above. Nonetheless, the overall incidence of toxicity grade 2 or above was significantly lower in the HA group than in the non-HA group (2.08% vs. 12.8%; OR: 6.88; $p<0.05$) (see Fig. 2). This finding was confirmed in the multivariate tests in which, after controlling for the rest of the factors, the inverse relationship between HA and overall toxicity ≥2 rose to an OR: 9.90 [95% CI: 1.02–100]; ($p<0.05$). None of the other factors studied were associated with the incidence of toxicity grade 2 or above.

Safety

The treatment with intravesical instillation of HA was safe. No related adverse effects were reported and the procedure was performed when the routine bladder catheterisation was done, in order to calculate the dose delivered to the bladder in BT.

Survival

The mean follow-up in the sample as a whole was 32.6 months. The mean (SD) disease-free survival was 58.41 (2.71) months and overall survival 59.80 (2.57) months. The comparison between groups (HA group vs. non-HA group) did not show significant differences either for disease-free survival (mean: 58.1 vs. 56.97 months; n.s.) or for overall survival (mean: 60.73 vs. 57.05 months; n.s.).

Discussion

The inflammation of the bladder epithelium following irradiation produces alterations in its permeability barrier, whose main function is to protect the underlying vesicular structures from substances in the urine which may cause damage and inflammation [8, 9].

HA is one of the GAG present on the surface of the bladder, where it interacts with other proteoglycans and with collagen to provide the extracellular matrix with stability and elasticity. Its presence impedes the spread of macromolecules and foreign bodies and thus represents an effective barrier [10].

In addition to the protection it affords to the extracellular matrix, HA participates in numerous physiological events such as cell adhesion, migration and proliferation. It also has anti-inflammatory, anti-oedematous and cicatrising properties. These effects have been reported in digestive and gynaecological surgery studies in patients undergoing various therapeutic procedures [11, 12]. The prophylactic use of a cream with HA is shown to reduce the incidence of high-grade radio-epithelitis [13] and it can provide an effective option for managing radiation dermatitis [14].

Acute radio-induced cystitis is a frequent complication in treatments that involve pelvic radiotherapy, with an incidence ranging between 23% and 80%. This form of the condition is associated with patient-related factors (diabetes, high blood pressure, previous pelvic surgery), tumour type and stage, radiotherapy (PTV, total bladder dose, association with BT) and chemotherapy. Late radio-induced cystitis is less frequent; its incidence ranges between 5% and 10% depending on the series consulted and the classification system used [1].

In urology, vesical instillations of HA have been used to treat interstitial cystitis. Several studies have shown that the replenishment of GAG via the administration of exogenous HA is able to reduce pain and urinary urgency in patients with interstitial cystitis [4, 15–17]. Another study has shown that intravesical instillations of HA are effective in preventing urinary infections in patients receiving palliative radiotherapy for vertebral metastases and medullar compression [18].

In an earlier 3-month follow-up study with 90 patients receiving 3DCRT and BT for cervix cancer between 2001 and 2002, we demonstrated that weekly instillation of HA exerted a protective effect on the bladder, reducing the incidence and grade of radio-induced cystitis and the risk of infection as well.

In the current study we found that the instillation of HA in cases of acute toxicity significantly reduces the incidence of radio-induced cystitis after the second and fourth sessions of BT. This effect is powerful and independent of factors such as tumour type, FIGO stage, ERT, chemotherapy and total dose of BT. In addition, we observed a trend towards a reduction in late toxicity, though it did not reach statistical significance: that is, in the period between six months after the end of treatment and the end of follow-up no patients in the HA group presented bladder toxicity, compared with 3 patients in the non-HA group. Another of the effects of HA demonstrated here is the significant reduction in the percentage of patients with toxicity grade 2 or above, the risk being several times lower than in the non-HA group.

Another factor shown to be associated with acute toxicity was 3DCRT. 3DCRT significantly increased the risk of acute toxicity after the third control session, irrespective of other factors.

The other factors studied –tumour type, FIGO stage and chemotherapy– did not present significant associations

with the appearance of acute bladder toxicity, late toxicity, or toxicity grade 2 or above.

Finally, the survival study shows that there were no significant differences in overall survival and disease-free survival comparing the two treatment groups, though overall survival was higher in the HA group. These results demonstrate that HA instillations do not compromise patient survival.

Conclusion

Vesical instillations of HA decrease the incidence and the degree of acute vesical toxicity induced by high-dose BT, and reduce the percentage of patients that develop toxicity of degree 2 or more. HA instillations are safe and do not compromise patient survival, but further confirmation in a randomised trial is needed.

Acknowledgements The authors thank Laboratorios Rubió, S.A., Castellbisbal, Barcelona, Spain for logistical support and also for providing funding for external technical assistants to carry out statistical analyses. Laboratorios Rubió, S.A. played no role in the study design or execution or analysis and interpretation of the data. Cystistat® is the property of Bioniche Pharma Group Limited and is distributed in Spain by Laboratorios Rubió, S.A.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

References

1. Marks LB, Carroll PR, Dugan TC et al (1995) The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 31:1257–1280
2. Nickel CJ, Cornish J (1994) Ultrastructural study of an antibody-stabilized bladder surface: a new perspective on the elusive glycosaminoglycan layer. Word J Urol 12:11–14
3. Hurst RE (1994) Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. World J Urol 12:3–10
4. Morales A, Emerson L, Níkel JC (1997) Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology 49:111–113
5. Kyker KD, Coffman J, Hurst RE (2005) Exogenous glycosaminoglycans coat damaged bladder surfaces in experimentally damaged mouse bladder. BMC Urol 5:4
6. Delgado JM, Samper P, Garrido J (2003) Hyaluronic acid in the prevention of radiation-induced cystitis (Abst.). Proc Am Soc Clin Oncol 22:752
7. Cox JD, Stetz J, Pajak TF (1995) Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341–1346
8. Kanai AJ, Zeidel ML, Lavelle JP et al (2002) Manganese superoxide dismutase gene therapy protects against irradiation-induced cystitis. Am J Physiol Renal Physiol 283:F1304–1312
9. Kanai A, de Groat W, Birder L et al (2006) Symposium report on urothelial dysfunction: pathophysiology and novel therapies. J Urol 175:1624–1629
10. Parsons CL, Boychuk D, Jones S et al (1990) Bladder surface glycosaminoglycans: an epithelial permeability barrier. J Urol 143:139–142
11. Kramer K, Senninger N, Herbst H et al (2002) Effective prevention of adhesions with hyaluronate. Arch Surg 137:278–282
12. Kusunoki M, Ikeuchi H, Yanagi H et al (2005) Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: a prospective randomized clinical trial. Surg Today 35:940–945
13. Liguori V, Guillemin C, Pesce GF et al (1997) Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. Radiother Oncol 42:155–161
14. Primavera G, Carrera M, Berardesca E et al (2006) A double-blind, vehicle-controlled clinical study to evaluate the efficacy of MAS065D (XClair), a hyaluronic acid-based formulation, in management of radiation-induced dermatitis. Cutan Ocul Toxicol 25:165–171
15. Kallestrup EB, Jorgensen SS, Nordling J et al (2005) Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. Scand J Urol Nephrol 39:143–147
16. Constantinides C, Manousakas T, Nikolopoulos P et al (2004) Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. BJU Int 93:1262–1266
17. Riedl CR, Engelhardt PF, Daha KL et al (2008) Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct 19:717–721
18. Mañas A, Glaria L, Peña C et al (2006) Prevention of urinary tract infections in palliative radiation for vertebral metastasis and spinal compression: a pilot study in 71 patients. Int J Radiat Oncol Biol Phys 64:935–940