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Efficacy of sodium hyaluronate in the management of chemical and radiation cystitis

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Onset of cystitis in patients receiving immuno-chemotherapeutic agents by intravesical instillation for non-muscle invasive transitional cell carcinoma of the bladder or after radiotherapy for prostatic cancer is frequent and problematic, since it responds poorly and slowly to the usual symptomatic treatments. This iatrogenic complication often means that cancer therapy has to be interrupted on account of the bladder pathology symptoms and of course this has further clinical implications. The symptoms resemble those of the urgency/frequency and painful bladder syndromes, so we tested the treatment used for these disorders to see whether it helped in this difficult clinical situation. This prospective study therefore enrolled 69 male consecutive patients, between 54 to 81 years of age, with iatrogenic acute cystitis; in 15 the symptoms had appeared after radiotherapy for prostatic cancer, in 24 after intravesical BCG, in 30 after instillation of Mitomycin C (with Synergo thermotherapy for 12 of them). All patients were given intravesical instillations of sodium hyaluronate, 40 mg/50 mL, weekly for from 8 to 24 weeks, depending on how the symptoms released. In the first four weeks dexamethasone 32 mg was mixed in as a "cocktail", on account of its prompt and effective topical antiinflammatory action and good mucosal penetration. Longer use of cortisone is contraindicated because of the high risk of sensitization and it provided no evidence of any ability to overcome the severe urinary disturbances with lasting effect. In order to allow patients with marked overactive bladder to keep these drugs within the bladder, we instilled lidocaine 2% 30 mL, 30 minutes before. Patients recorded their bladder capacity (BC) by filling a micturition diary. Pain was assessed using a Visual Analog Scale (VAS) from 0 to 10 for the chemical cystitis cases at the beginning and end of treatment. After only four weeks BC increased in all patients, and urgency and pain disappeared. Treatment was continued, however, for another four weeks, even in patients with total remission of their symptoms as we had seen earlier that if it was stopped too soon the symptoms could return. In the chemical cystitis group the VAS score dropped from an initial mean of 8.6 to 0.9 at the end of treatment (P<0.0001). Mean BC rose from 58.4 to 283.7 mL in the chemical cystitis cases (P<0.0001), and from 85 to 243.3 mL (P<0.0001) in the radiotherapy patients. Overall 67 patients (97%) reported complete relief of dysuria and pain. Two treatment failures were due to a reduced compliance to treatment by the patients themselves. No adverse reactions were observed related to the catheters or drugs used. Patients with non-invasive bladder tumors were able to restart their cancer therapy. For cystitis induced by intravescical immuno-che-

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motherapy or pelvic radiotherapy this approach appears to achieve an effective and rapid cure with no adverse reactions, allowing the conclusion of treatments for non-invasive transitional cell-bladder cancer. Patients with chemical cystitis responded a little better than those who had received radiotherapy. Subsequent urinary cytology and cystoscopy ruled out bladder cancer progression in these cases after temporary postponement of the oncological treatment. Intravescical sodium hyaluronate seems a valid and quick therapeutic solution for iatrogenic cystitis from chemo or radiotherapy. After review literature, this strategy does not appear to have been used before for this particular problem.

Key words: **Urinary bladder neoplasms - Cystitis - Mitomycin C - Radiotherapy - Hyaluronic acid.**

Iatrogenic cystitis arising after intravesical chemo or immunotherapy for transitional cell bladder cancer, or radiotherapy can often prove disabling; treatment is a problem because the symptoms respond poorly to the usual symptomatic drugs and often oblige the patient to interrupt cancer therapy.

The initial symptoms are pelvic pain, frequency, urgency, painful micturition and even urge- incontinence and hematuria in the most acute forms. The patient reduces the fluid intake in an attempt to overcome the frequency and pain, so the concentration and acidity of the urine rise, making the burning sensation worse.

Treatment usually involves oral analgesics, anti-inflammatory drugs, antispastics and cortisone for the most acute situations.

These do achieve some gradual improvement, but it may take weeks in the mild forms and months for more severe ones, especially after radiotherapy. It is also often essential to interrupt antitumoral therapy, as any attempt at restarting it leads to the reappearance of symptoms – often more serious than before.

Different treatment strategies have been attempted to manage this disease particularly in radiation cystitis with important bleeding.

Cystoscopy with laser fulguration or elettrocoagulation of bleeding points is sometimes effective.[1] Injection of botulinum toxin A in the bladder wall can achieve moderate to severe improvement.[1, 2] Oral sodium pentosan polysulphate must be administered for a long time in order to prevent further recurrence of hemorragic cystitis associated with pelvic radiotherapy.[3] Two case reports show, in one case, successful use of intravesical aluminium and magnesium hydroxide gel,[4] while in the other case, after failure of the same treatment, cotton pledgets soaked in 5% formalin, placed endoscopically onto the bleeding sides of the bladder, were successful.[5] Controversial results were also obtained with hyperbaric oxygen.[6, 7] More aggressive treatment as laparoscopic cystoprostatectomy has been proposed as a last resort after unsuccessful conservative treatment.[8]

With a view to achieving faster and more lasting relief of the symptoms we decided to test a strategy used for the urgency/frequency and painful bladder syndromes, where in our hands it has given often definite improvement in symptoms.[9] This treatment uses intravesical instillations of sodium hyaluronate and cortisone, and quickly resolves the acute inflammation.

Materials and methods

This is a prospective study of 69 male consecutive patients between 54 and 81 years of age, who had been receiving intravesical immuno-chemotherapy for non invasive transitional cell carcinoma of the bladder or radiotherapy for prostatic cancer and had presented symptoms of cystitis with severe complaint. In 24 the symptoms had arisen after weekly intravesical instillations of BCG for high-grade G2-3 bladder cancers, 13 pT1 with non muscle invasion at second look, and 11 pTa; 12 others had been receiving weekly instillations of Mitomycin C 40 mg with hyperthermia and Synergo technology [10] for transitional cell bladder cancers, G2-3 pT1 in four cases, pTa in 7 and Cis in 1; 18 had been treated with intravesical Mitomycin C 40 mg for low-grade bladder tumors: relapsing G1-2 and/or multifocal pTa in 9, pT1 in 7 and high-grade G3 pTa in two who did not tolerate BCG and

refused cystectomy. The cystitis symptoms usually became evident at the third or fourth drug dose. In 15 patients symptoms had appeared after radiotherapy for prostatic adenocarcinoma.

Almost all patients complained of intense and troublesome frequency with urgency, with or without a burning sensation on urination and/or suprapubic pain that got worse as the bladder filled. Ten also had urge-incontinence.

In the patients with chemical cystitis we assessed the pain using a Visual Analogue Scale (VAS) from 1 to 10, in which 10 indicated maximum pain tolerated. We did not use the VAS in the ex-radiotherapy patients whose discomfort was mainly related to frequency and urgency incontinence. Bladder capacity (BC) was calculated in all patients as the mean of urinary volumes recorded by each patient in a diary, for at least two days.

Some were not able to measure the urine volume because the almost continuous urgency obliged them to wear a pad, and in these cases BC was indicated as 10 mL.

After full informed consent, all patients were given four weekly intravesical instillations of hyaluronic acid 40 mg diluted in 50 mL and dexamethasone 32 mg, to be held in the bladder for one hour. After these four weeks only sodium hyaluronate 40 mg/50 mL was instilled. When symptoms were particularly acute oral analgesics and antispastics were also provided and if necessary the penis was clamped to keep the solution in the bladder. In order to allow patients with marked overactive bladder to keep these drugs within the bladder, we instilled lidocaine 2% 30 mL, 30 minutes before.

At the end of the first month treatment, patients with chemical cystitis re-assessed their pain on the VAS. BC was estimated again for all patients, using the micturition diaries.

Results

Symptoms were quickly relieved after the first four instillations in almost all the patients.

TABLE I.—*VAS scores before and after treatment in patients with chemical cystitis.*

	VAS		
No. patients	Before	After	Differences
1	7	1	-6
2	7	1	-6
3	10	0	-10
4	5	0	-5
5	7	2	-5
6	10	3	-7
7	8	2	-6
8	9	3	-6
9	7	0	-7
10	8	1	-7
11	8	2	-6
12	7	0	-7
13	8	3	-5
14	9	2	-7
15	7	0	-7
16	8	0	-8
17	10	2	-8
18	10	0	-10
19	10	2	-8
20	10	3	-7
21	7	N.E	N.E
22	9	2	-7
23	10	0	-10
24	9	0	-9
25	10	0	-10
26	9	1	-8
27	9	0	-9
28	10	0	-10
29	9	0	-9
30	8	1	-7
31	9	1	-8
32	10	2	-8
33	7	0	-7
34	9	0	-9
35	8	1	-7
36	10	3	-7
37	9	0	-9
38	7	N.E	N.E
39	10	0	-10
40	10	0	-10
41	9	2	-7
42	7	1	-6
43	8	0	-8
44	9	0	-9
45	9	2	-7
46	10	1	-9
47	7	1	-6
48	9	1	-8
49	10	2	-8
50	8	0	-8
51	6	0	-6
52	9	1	-8
53	10	0	-10
54	9	0	-9
Mean	8.6	0.9	-7.7
Median	9	1	-8

Paired t-test: T= -38.09 P<0.0001
95% CI of mean change: -8.12 and -7.31.

TABLE II.—*Bladder capacity before and after treatment in patients with chemical cystitis.*

	Bladder capacity(mL)		
No. patients	Before	After	Changes
1	10	200	190
2	10	180	170
3	50	250	200
4	10	220	210
5	30	250	220
6	50	300	250
7	50	250	200
8	30	280	250
9	80	350	270
10	10	250	240
11	100	400	300
12	90	350	260
13	90	300	210
14	100	400	300
15	50	200	150
16	80	250	170
17	150	300	150
18	20	200	180
19	100	400	300
20	100	500	400
21	80	N.E.	N.E.
22	40	200	160
23	20	100	80
24	60	250	190
25	54	300	246
26	50	250	200
27	65	200	135
28	70	200	130
29	40	150	110
30	60	150	90
31	50	250	200
32	10	250	240
33	100	300	200
34	30	250	220
35	100	380	280
36	10	270	260
37	50	320	270
38	80	N.E	N.E.
39	40	370	330
40	20	400	380
41	60	420	360
42	100	380	280
43	80	320	240
44	40	290	250
45	20	300	280
46	80	250	170
47	55	280	225
48	120	340	220
49	40	200	160
50	10	190	180
51	70	340	270
52	80	300	220
53	110	400	290
54	50	320	270
Mean	58.4	283.7	266.1
Median	52	280	220

Paired t-test: T= 23.96, P<0.0001
95% CI of mean change: 207.1 and 245 mL.

TABLE III.—*Patients' bladder capacity before and after radiotherapy cystitis.*

	Bladder capacity(mL)		
No. patients	Before	After	Changes
1	50	200	150
2	80	230	150
3	85	270	185
4	70	220	150
5	110	260	150
6	90	200	110
7	140	290	150
8	100	210	110
9	60	250	190
10	90	270	180
11	110	230	220
12	50	250	200
13	85	280	195
14	95	290	195
15	60	200	140
Mean	85	243.3	165
Median	85	250	150

Paired t-test T=19.45, P<0.0001; 95% CI of mean change: 146.8 and 183.2 mL.

Table I shows patients' pain scores on the VAS before and after two months treatment: the initial mean score of 8.6 dropped to 0.9 with evidence of a marked improvement. Comparing these scores with the t-test for paired data, the mean difference is -7.7 points, with a 95% confidence interval (CI) of -8.12 and -7.31; P<0.0001.

BC also improved in all cases, and Tables II, III list the individual values and means before and after treatment. Patients with chemical cystitis had greater improvement, with mean BC rising from 58.4 to 283.7 mL (mean difference 226.1 mL; 95% CI 207.1 and 245 mL; t test for paired data 23.96, P<0.0001); in patients who had had radiotherapy mean BC rose from 85 to 243.3 mL (mean difference 165; 95% CI 146.8 and 183.2 mL, P<0.0001).

We report two treatment failures due to high grade bladder overactivity with inability to keep the drugs in the bladder for more than 10 minutes.

The other patients felt complete relief from their urinary symptoms and pain, and could re-start their chemotherapies, completing the scheduled protocols.

Discussion and conclusions

When symptoms of cystitis arise during intravesical immuno-/chemotherapy for non-invasive transitional cell bladder tumors, the treatment has often to be stopped; this has important impact on the possibility of success, and it can make radical surgery essential. If the symptoms can be resolved promptly the patient not only feels subjectively better but also may be able to complete the tumor therapy, with obvious consequences as regards morbidity and present and future quality of life.

As the symptoms tend to be similar to those of the urgency/frequency and painful bladder syndromes, also referred to as interstitial cystitis, we tested the same therapy for patients with symptoms of iatrogenic cystitis (secondary to intravesical therapies or radiotherapy) that made it impossible to continue chemotherapy despite antibiotics, antispastics and analgesics. Relief was detectable after only four intravesical instillations of sodium hyaluronate with dexamethasone, and this was consolidated when treatment was continued for at least other four weeks; then these patients were able to restart their cancer therapies. The subjective findings were confirmed by the significant increases in BC and the reductions in VAS scores for pain.

This therapeutic strategy therefore seems particularly indicated in the unusual clinical situations where patients respond poorly to routine symptomatic treatments and have to stop a valid oncologic therapeutic schedule. In the literature we found no reports of this treatment having been used to date in similar cases.

Riassunto

Valutazione dell'efficacia dello ialuronato di sodio nel trattamento delle cistiti chimiche e attiniche

L'insorgenza di sintomatologia cistitica durante instillazioni vescicali con immuno-chemioterapico per il trattamento del tumore uroteliale vescicale non muscolo invasive o dopo trattamenti radioterapici per la cura della neoplasia prostatica, rappresenta una situazione clinica frequente e di difficile risoluzione in quanto poco responsiva ai comuni trattamenti sintomatici adottati. Inoltre il verificarsi di questa patologia iatrogena comporta quasi sempre l'interruzione del trattamento oncologico per la patologia vescicale con ulteriori implicazioni cliniche. La similitudine della sintomatologia con quella che si verifica nella sindrome urgenza/frequenza o dolorosa vescicale, ci ha indotti ad utilizzare lo stesso trattamento (ialuronato di sodio) per osservarne l'effetto in una così impegnativa situazione clinica. Abbiamo così attuato uno studio prospettico di 69 pazienti di sesso maschile di età compresa fra 54 e 81 anni in cui era insorta una cistite acuta iatrogena: in 15 pazienti dopo radioterapia per il trattamento della neoplasia prostatica, in 24 dopo instillazione endovescicale con BCG e in 30 dopo instillazione con Mitomicina C (di cui 12 casi associati a termo chemioterapia con tecnologia Synergo). Tutti i pazienti sono stati trattati con instillazioni endovescicali di ialuronato di sodio 40 mg/50 ml con cadenza settimanale per una durata complessiva del trattamento compresa tra 8-24 settimane in base alla remissione totale dei sintomi. Nelle prime quattro settimane all'acido ialuronico si è associato desametasone 32 mg in "cocktail" per la sua spiccata e veloce attività antiinfiammatoria anche topica e la buona penetrabilità attraverso le mucose. Tuttavia, l'uso prolungato del cortisonico è controindicato perché espone ad alto rischio di fenomeni di sensibilizzazione ed il suo uso,in passato,si è dimostrato comunque insufficiente a risolvere la sintomatologia disurica grave e a mantenere nel tempo gli effetti ottenuti. Per far trattenere i farmaci in vescica in pazienti con spiccata iperattività vescicale abbiamo provveduto ad instillare in vescica Lidocaina 2% 30 ml, 30 minuti prima del cocktail. Abbiamo valutato la capacità vescicale (CV) in tutti i pazienti mediante registrazione del diario minzionale, mentre il dolore è stato valutato, attraverso un Visual Analog Scale (VAS) da 0 a 10, solo nei casi con cistite chimica all'inizio ed alla fine del trattamento. Già dopo quattro settimane abbiamo riscontrato in tutti i pazienti un aumento della CV con scomparsa dell'urgenza minzionale e del dolore. Tuttavia il trattamento è proseguito per almeno altre quattro settimane anche in coloro in cui la remissione dei sintomi era totale in quanto abbiamo osservato in precedenza che la sospensione anticipata del trattamento poteva comportare una ripresa della sintomatologia. Nei casi di cistite chimica il VAS si è ridotto da un valore medio iniziale di 8.6 ad un valore finale di 0.9 ($P<0,0001$). La CV media, nelle cistiti chimiche, è aumentata da 58.4 a 283.7 ml ($P<0,0001$), mentre nei casi di cistite attinica la CV media è aumentata da 85 a 243.3 ml ($P<0,0001$). In 67 pazienti (97%) si è osservata la completa remissione della sintomatologia disurica dolorosa. In due casi si è dovuto sospendere il trattamento a causa di un'insufficiente compliance alla terapia dello stesso paziente. Non sono stati osservati effetti collaterali legati al cateterismo o ai farmaci usati. Tutti i pazienti, affetti da neoplasia vescicale non invasiva, sono risultati in grado di riprendere successivamente la terapia oncologica interrotta. In conclu-

sione possiamo ritenere questo trattamento un'opzione valida ed efficace, oltre che priva di effetti collaterali, per ottenere una rapida guarigione della cistite iatrogena indotta sia dalla somministrazione endovescicale di farmaci immunochemioterapici che da trattamenti radioterapici dello scavo pelvico; inoltre si è dimostrata un'arma terapeutica utile a favorire il completamento delle cure non cruente per la neoplasia vescicale uroteliale non muscolo-invasiva. Da ultimo vogliamo comunque segnalare che una migliore risposta al trattamento è stata rilevata nei casi di cistite chimica rispetto a quelli dopo radioterapia. Il controllo con la citologia urinaria e la cistoscopia non hanno dimostrato una progressione della neoplasia, nonostante la temporanea sospensione della terapia oncologica. Da una revisione della letteratura scientifica non risulta che tale trattamento sia mai stato impiegato fino ad ora per trattare casi analoghi. Messaggio conclusivo: riteniamo la terapia topica endovescicale con ialuronato di sodio una valida opzione terapeutica nel trattamento delle cistiti iatrogene siano esse di origine chimica o attinica.

Parole chiave: Neoplasia vescicale - Cistite - Mitomicina C - Radioterapia - Acido ialurinico.

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