Cancer Chemother Pharmacol (1983) 11 (Suppl): S 91–S 93

Cancer Chemotherapy and Pharmacology

Bladder instillation of Adriamycin in the treatment of bladder cancer

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Summary. *Intravesical Adriamycin instillation was used in 10 patients with transitional cell carcinoma of the bladder as postoperative prophylactic treatment against recurrence.*

The protocol for bladder instillation was 20 mg/10 ml of Adriamycin twice weekly for a total of eight doses.

One patient developed recurrence in 3 months and three, in 6 months. The main local side-effects were frequency and dysuria which occurred in four cases. Leukopenia and increased SGOT and SGPT values each occurred in one case. No cases of cardiotoxicity, fibrosis, or atrophy of the bladder mucosa were found. Further studies are necessary to achive the best possible results.

Introduction

The propensity for bladder cancer to recur is well known [6, 10, 11]. An effective antineoplastic agent to prevent recurrence or to prolong the interval between recurrences would be useful to the urologist. Intravesical administration of an antineoplastic agent ensures that a high concentration of the drug is in contact with the neoplastic cells, while minimizing systemic toxicity.

Numberous agents have been used with variable degrees of success and toxicity [9, 14–16, 18–21].

Intravesical Adriamycin instillation has been used for treatment and for prevention of recurrence of transitional cell carcinoma [2, 8, 20] on account of the mild local irritation and negligible plasma uptake with high uptake into the urothelium [7].

Our clinical experience with intravesical instillation of Adriamycin for the treatment of bladder cancer is presented in this paper.

Materials and methods

Between December 1981 and April 1982, 12 patients underwent intravesical Adriamycin instillation postoperatively to prevent recurrence of bladder cancer.

All patients had had prior surgical treatment, and transitional cell carcinoma had been proven histologically. One week after operation, the patients were asked to lie on the examination table after voiding urine, and 20 mg Adriamycin in 10 ml distilled water was instilled into the bladder through a sterile catheter.

The catheter was then removed and the patient was instructed to retain the medication for more than 2 h and change position every 15 min.

This procedure was performed twice weekly a total of eight times. During this study, one patient dropped out after only three instillations and another was lost to follow-up; all the others received the full quota of eight instillations and were subsequently followed-up by cystoscopy at 3-month intervals.

Table 1. Clinical data and recurrence

Case	Stage[a]	No. of tumors	Status[b]	Size (cm)	Treatment[c]	Recurrence	
						3 months	6 months
1	$>B_1$	1	2	3–4	part	(−)	(+)
2	A	1	1	1–2	TVC	(−)	(−)
3	$>B_1$	1	1	3–4	TUR	(+)	(+)
4	A	1	1	1–2	part	(−)	(−)
5	A	1	2	1	TUR	(−)	(−)
6	$>B_1$	3	2	3–4	TUR	(−)	(−)
7	A	4	2	1	TVC	(−)	(−)
8	$>B_1$	2	1	3–4	part	(−)	(−)
9	$>B_1$	1	2	3–4	part	(−)	(+)
10	0	1	1	1	TVC	(−)	(−)

[a] Jewett's classification

[b] 1, primary tumor; 2, recurrent tumor

[c] Part, partial cystectomy; TVC, cystotomy + cauterization; TUR, transurethral resection

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Their ages ranged from 47 to 69, with a mean of 58.5 years.

There were seven men and three women.

The patients were evaluated by physical examination, excretory urography, endoscopy, ECG, routine hematological and biochemical determinations, T cell, B cell, active T cell, and PHA tests, and checks of bladder and general symptoms.

Results

After eight intravesical instillations of Adriamycin, one case of recurrent bladder tumor was observed at the 3-month follow-up and three cases at 6 months (Table 1).

The hematogram, and the electrolyte, renal function, and liver function tests had no changed significantly after the therapy.

One patient, however, had leukopenia (WBC 2,850/mm^3) after five instillations. The WBC rose again to more than 4,000/mm^3 after discontinuation of the treatment for 2 weeks, and the residual three instillations were performed without any significant change.

One patient had elevated GOT and GPT levels during therapy.

The T cell, B cell, active T cell, and PHA levels were not significantly depressed after therapy (Table 2).

Side-effects taking the form of subjective symptoms were minor; there were three cases of general malaise, one of numbness of the hands, four of pain on micturition and frequent urination, and two of nausea and anorexia (Table 3). All these were transient and the patients recovered without any residual symptoms.

No stomatitis, alopecia, or fibrosis or atrophy of the bladder mucose was found.

Table 2. Results of B cell, T cell, active T cell, and PHA tests

Case	1	5	6	7	8	9
B cell (%)						
Before	31.6	20.6	32.3	27.3	27.0	19.0
After	15.6	21.5	23.2	18.3	24.1	42.0
T cell (%)						
Before	65.1	63.6	68.4	76.7	73.4	53.0
After	62.7	55.4	64.2	69.3	58.3	48.7
Active T cell (%)						
Before	20.2	11.6	18.5	13.5	10.1	
After	16.0	4.0	6.6	25.0	7.7	14.2
PHA index						
Before	4.82	18.0	16.8	10.6		10.7
After	27.80	3.56	4.7	18.5	24.3	11.8

Table 3. Side-effects in 10 patients

Micturition pain	4
Frequent urination	4
General malaise	3
Anorexia	2
Nausea	2
Leukopenia	1
Increased GOT, GPT	1
Total	11 cases

Discussion

The use of topical bladder instillation is well documented as a therapeutic approach to prevention of recurrence.

Intravesical cytotoxic drug instillation is not without danger, local and systemic side-effects having been reported frequently [15, 16, 19].

Thio-TEPA is the compound most frequently used for intravesical chemotherapy. As it causes myelosuppression as a side-effect, thio-TEPA is not an ideal drug and other agents are being investigated.

Adriamycin is a potent antineoplastic agent against various tumors [3]. It is well tolerated by bladder mucosa when administered topically. Topically administered Adriamycin is able to penetrate into intact urothelium by overcoming the asymmetric unit of the membrane and the tight junction. Exophytic papillary tumors show the highest uptake, presumably because of the large surface area in relation to tissue volume [7].

Banks et al. [2] and many other authors [8, 17, 20] have demonstrated high response rates in patients with transitional cell carcinoma treated topically.

The major complications of Adriamycin therapy have been cardiotoxicity, myelotoxicity, and gastrointestinal disturbances, etc. [3].

In our clinical experience, the drug has been a mild irritant to bladder; four patients had local symptoms such as frequent urination and dysuria. These did not present a problem.

Cardiotoxicity has not been noted in our series. Myelotoxicity was found in one case with leukopenia (WBC down to 2,850/mm^3), which normalized after discontinuation of the drug instillations for 2 weeks. Thus, myelosuppression may be caused by the absorption of drug from the bladder mucosa through the muscle layer in the case of deep infiltrating tumors. But it is mild compared with that caused by thio-TEPA.

Gastrointestinal upset was noted in two cases, but was transient.

In general, intravesical Adriamycin instillation was well tolerated and did not incapacitate any of the patients.

Lymphocyte count and immunocompetence were correlated with prognosis and stage in bladder tumor [1, 4, 5, 12]. No rebound improvement of lymphocyte reactivity occurred in patients following successful operation for the tumors [13]. Any change in lymphocyte reactivity must therefore be induced by chemotherapy or other factors.

Adriamycin is a cytotoxic antibiotic, but results of the T cell, B cell, active T cell, and PHA tests are not significantly changed after intravesical therapy and there was no correlation between these results and stage in our series.

One case of recurrent bladder tumor was found at the 3-month follow-up cystoscopy. It was encrusted over, and not the 'cauliflower' type as before. There were three recurrent bladder tumors at 6 months.

The recurrence rate of bladder cancer was influenced by the initial stage, grade, number, and size of bladder tumors [6, 11]. There have been reports to the contrary, however [10].

In our series, recurrence was connected with initial stage, number, and size of the bladder tumors.

The effect of Adriamycin in treatment of bladder cancer must be examined in more extensive clinical studies, since our experience is relatively short and our series contained too few patients for a definitive conclusion to be possible.

This drug should be further studied to find how the best possible results can be achieved.

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