Cancer Chemother Pharmacol (1987) 20 (Suppl): S 60–S 62

Cancer Chemotherapy and Pharmacology

Intravesical chemotherapy

Tsuneaki Obama, Yosuke Matsumura, Hiroyuki Ohmori, and Okayama Urological Cancer Collaborative Group (OUCCG)

Department of Urology, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700, Japan

Summary. A total of 85 cases treated by intravesical administration of adriamycin (ADM) at Okayama University and other cooperating institutions were examined. Instillation of 50 mg adriamycin dissolved in 30 ml physiological saline was performed in two courses of 3 consecutive days, with a 4-day interval between the courses. The response rate was 70.6%. Following instillation therapy transurethral resection (TUR) was carried out in 69 cases (80%), segmental cystectomy in 7, and total cystectomy in 3. The follow-up period averaged 42 months, during which the recurrence rate was 57%; recurrence occurred within 18 months in 80% of these cases. Since the recurrence per patient-month × 100 was 3.348, the precise effect of intravesical chemotherapy in the prevention of recurrence was unclear. There were 9 cases of advanced disease (11% of the total, 18% of cases with recurrence). One patient with CIS (flat invasive tumor) seemingly achieved CR, but died 43 months after treatment due to metastatic disease. While this method is not always indicated in cases of CIS (flat invasive tumor), in cases in which it is indicated a drug causing only limited stimulation of the bladder mucosa should be used and long-term follow-up is essential.

Introduction

Many drugs have been evaluated for the intravesical instillation chemotherapy of superficial bladder tumors [1–9]. However, although the effectiveness of such methods for the prevention of recurrence has been recognized, the role of such treatment against bladder cancer has not yet been confirmed. In order to clarify this point the authors evaluated the results of intravesical instillation of adriamycin in 85 cases from the following aspects: (1) Indications and purpose; (2) limitation; (3) drug selection; (4) therapeutic schedule.

Materials and methods

As shown in Table 1, the present study was conducted in 85 cases of superficial bladder cancer treated at Okayama University School of Medicine and other cooperating institutions in the OUCC group. There were 74 male and 11 female patients, 64 with primary tumors and 21 with recurrent tumors. In 80 cases (94.1%) the tumors were 3 cm or less in size and in 76 cases (89.4%) the tumors were papillary. Stage T_1 or T_a cases accounted for 79 cases (92.9%), and 73 patients (85.9%) had grade 1 or 2 tumors (Table 2).

Instillation of 50 mg adriamycin dissolved in 30 ml physiological saline was performed on 3 consecutive days, with a 4-day interval between the first and second courses. In 79 cases (92.9%) ten instillations or fewer were administered.

Table 1. Tumor

Primary	64 (75.3%)		
Recurrent	21 (24.7%)		
Single	24 (28.2%)		
Multiple	61 (71.8%)	2	13 (21.3%)
		3	13 (21.3%)
		4	5 (8.2%)
		5≦	30 (49.2%)
Size			
<1 cm	39 (45.9%)		
1≦ <3 cm	41 (48.2%)		
3 cm≦	5 (5.9%)		
Shape			
papillary	76 (89.4%)		
sessile	7 (8.2%)		
flat	1 (1.2%)		
others	1 (1.2%)		

Table 2. Stage and grade

Stage	
TA	25 (29.4%)
Tl	54 (63.5%)
Tis	1 (1.2%)
Others	4 (4.7%)
TX	1 (1.2%)
Grade	
Gl	36 (42.4%)
G2	37 (43.5%)
G3	7 (8.2%)
GX	5 (5.9%)

Table 3. Response

CR	9 (10.6%)
PR	51 (60.0%)
NC	22 (25.9%)
PD	2 (2.4%)
unknown	1 (1.2%)

Offprint requests to: Y. Matsumura

Table 4. Toxicity

	Irritability	Macrohematuria	Infection	Total
Grade 1	30 (60.0%)	2 (50.0%)	0	32
Grade 2	12 (24.0%)	1 (25.0%)	1 (100.0%)	14
Grade 3	8 (16.0%)	1 (25.0%)	0	9
Total	50	4	1	55

Table 5. Local recurrence (times)

0	36 (42.4%)
1	18 (21.2%)
2	12 (14.1%)
3	6 (7.1%)
4	4 (4.7%)
5	5 (5.9%)
6≦	3 (3.5%)
Unknown	1 (1.2%)

Table 6. Follow-up treatment

None	59 (69.4%)
IVC	13 (15.3%)
Systemic Chemo	9 (10.6%)
RXT	2 (2.4%)
Others	2 (2.4%)
None	3 (3.5%)
TUR	69 (80.2%)
TVC	4 (4.7%)
SR	7 (8.1%)
TC	3 (3.5%)

Results

Results of treatment

Complete response (CR) was recognized in 9 cases and partial response (response of more than 50% but less than 100%; PR) in 51 cases; thus, the rate of effectiveness was 70.6% (Table 3).

Side effects

Some side effects were recognized in 55 of the 85 cases (64.7%, Table 4). Most consisted in bladder irritation.

Recurrence

Recurrence was observed in 57% (recurrence in 48, unclear in 1), and the rate of recurrence is shown in Table 5. In 37 cases (77%) the recurrence was observed within 12 months.

Postprocedural courses

No previous treatment had been received in 59 cases, and in 69 cases (80.2%) residual tumor was treated by TUR (Table 6).

In 3 patients whose disease had advanced to T_3 total cystectomy was performed. One of these had more than five tumors and did not respond to treatment; in one other case a diagnosis of CIS was made and CR was recorded, but 31 months later progression to T_4 was seen; and in one other patient, who had multiple papillary, T_1G_2 disease, no effect was observed (Table 7).

There were 8 fatalities (Table 8), 2 in patients who had achieved CR but did not attend for follow-up right to the end of the study.

Discussion

Since Jones and Swinney [1] reported the effects of intravesical administration of thio-TEPA in 1961, many drugs have been used in this way. However, while this strategy

Table 7. Patients with total cystectomy

No.	Tumor				Response of IVC	Follow-up duration	Cause of death
	number	shape	grade	stage			
1	M	Pap	2	Tl	NC	36 M	ALive
2	M	Pap	2	Tl	NC	40 M	ALive
3	M	NNT	2	Tis	CR	43 M	Meta

Table 8. Mortality case

No.	Tumor				Response of IVC	Recurrence	Operation	Duration of follow-up (months)	Cause of death
	number	shape	grade	stage					
1	S	Pap	2	Tl	NC	1	TUR	12 M	Metastasis
2	M	Pap	2	Tl	NC	1	TUR	21 M	Metastasis
3	M	Pap	1	Tl	NC	3	TUR	27 M	Metastasis
4	M	Pap	2	Ta	NC	3	TUR	42 M	Metastasis
5	M	NNT	2	Tis	CR	4	TUR, total	43 M	Metastasis
6	M	Pap	2	Tl	NC	6≦	TUR	87 M	Rectal ca.
7	M	Pap	X	X	CR	5	TUR	38 M	Pneumonia
8	M	Pap	2	Tl	NC	0	TUR	14 M	Apo.

has been shown to be effective in preventing recurrence, the effectiveness of this method for primary bladder cancer has not been proved. As has been pointed out by Pavone-Macaluso [8], there are still many problems concerning intravesical instillation chemotherapy.

In other words: (1) Is a single instillation better than irrigation? (2) What criteria can be used for drug selection? (3) What is the best therapeutic schedule? (4) Is it possible to combine intravesical instillation and systemic chemotherapy? (5) Is it possible to combine intravesical instillation of chemotherapeutic agents with other methods of treatment (e. g., hyperthermia) to increase effectiveness. In addition, different standards are used for the evaluation of effectiveness by different investigators; therefore their data are not necessarily strictly comparable. Prospective randomized trials are necessary to solve these problems. The present report was compiled in an attempt to clarify these points, even to a limited extent.

1. Indications and purpose. Absolute indications for this therapy include bladder cancers characterized by (a) low-grade malignancy; (b) relatively early stage (T_a, T_1); (c) multiple location; and (d) size less than 1 cm. It is also important that transurethral curettage or resection, (TUC/TUR) be performed to debulk the tumor as much as possible. In other words, TUC or TUR may need to be performed for optimum results to be achieved with instillation therapy.

2. Limitations. When the above four conditions are not satisfied, it is necessary to realize that this method cannot bring about a cure, but only palliation. When tumors are 3 cm or more in size it is necessary to evaluate the degree of invasion carefully. This method is not considered to be indicated for carcinoma in situ.

3. Drug selection. It is necessary for any drug seriously considered (a) to be effective in transitional cell carcinoma; (b) to have a strong affinity for malignant tissue; (c) to have a marked cytocidal effect with a short contact time; and (d) to have a low level of transmission from the bladder mucosa to the blood stream. The drugs that satisfy the above conditions are MMC [4], ADM [2], 4'-epi-ADM [3], THP, and CQ [5]. The rates of effectiveness are 60%–80%, and side effects have been observed in 30%–50% of cases.

4. Drug administration. Complete response cannot be anticipated with ten or fewer instillations of drug, and it is necessary to complete the whole of the treatment within a short period.

Following the intravesical instillation of ADM in 85 cases of bladder cancer at Okayama University and other institutions, TUR was carried out as planned in 69 cases (80%), while in 3 cases total cystectomy was performed. Follow-up for an average of 42 months revealed recurrence in 57%, within 18 months in 80% of these, giving a rate of 3.348 for recurrences per patient-month $\times 100$; therefore it is not completely clear what influence intravesical instillation has on the prevention of recurrence. There were 9 cases of advanced disease (11% of the total and 18% of the recurrent cases). In one case of CIS (flat invasive tumor) a CR was obtained, but the patient died of metastatic disease 43 months after treatment. This treatment is not indicated in all cases of CIS, but when it is important to select a drug which has little stimulating effect on the bladder mucosa and also to evaluate the result of long-term follow-up observations in addition to the immediate effects.

References

1. Jones HC, Swinney J (1961) Thio-TEPA in the treatment of tumors of the bladder. Lancet II: 615
2. Matsumura Y, Ozaki Y, Ohmori H (1983) Intravesical adriamycin chemotherapy in bladder cancer. Cancer Chemother Pharmacol 11 [Suppl]: S69
3. Matsumura Y, Tsushima T, Ozaki Y, Yoshimoto J, Akagi T, Obama T, Nasu Y, Ohmori H (1986) Intravesical chemotherapy with 4'-epi-adriamycin in patients with superficial bladder tumors. Cancer Chemother Pharmacol 16: 176
4. Mishina T, Oda K, Murata S, Ooe H, Mori Y, Takahashi T (1975) Mitomycin C bladder instillation therapy for bladder tumors. J Urol 114: 217
5. Misaki T, Hisazumi H, Uchibayashi T, Taya T, Kuroda K (1980) The prophylactic use of carboquone and urokinase in bladder carcinoma. Acta Urol Jpn 26: 683
6. Niijima T, Matsumura Y, Kondo K, Katayama Y, Ozaki Y (1975) Intravesical instillation of adriamycin for the treatment of tumor of the bladder: The preliminary report. Acta Urol Jpn 21: 233
7. Ozaki Y (1977) Bladder instillation of adriamycin in the treatment of bladder tumors: 1. Clinical results. Jpn J Urol 68: 934
8. Pavone-Macaluso M, Ingargiola GB (1980) Local chemotherapy in bladder cancer treatment. Oncology 37 [Suppl 1]: 71
9. Shuin T, Moriyama M, Miura T, Kubota Y, Nishimura R, Takai S (1981) Our experience of intravesical instillation therapy for bladder cancer using aclacinomycin A. Acta Urol Jpn 27: 1119
10. Veenema RJ, Dean AL Jr, Uson AC, Roberts M, Longo F (1969) Thio-TEPA bladder instillation: therapy and prophylaxis for superficial bladder tumors. J Urol 101: 711