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SESSION III

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Intravesical instillation chemotherapy of Adriamycin with or without verapamil for the treatment of superficial bladder cancer: the final results of a collaborative randomized trial

Abstract A collaborative randomized clinical trial on the intravesical administration of Adriamycin (ADM) with or without verapamil (VR), a calcium-channel blocker, as chemotherapy of superficial bladder cancer (Ta, T1) was carried out at two universities, Okayama and Kagoshima, and their affiliated hospitals. Arm A consisted of ADM given at 50 mg/50 ml saline, and arm B consisted of ADM given at 50 mg/40 ml saline plus five ampules (25 mg/10 ml saline) of injectable VR. The drugs were instilled into the bladder for 3 consecutive days, and three such courses were given with a 4-day interval between each course for a total of nine instillations. A total of 96 patients (48 in arm A and 48 in arm B) were entered into this study. The two treatment groups showed no significant difference in backgound factors. Of the 40 evaluated arm-A patients, 24 (60.0%) showed a response (CR+PR), whereas 19 (48.7%) of the 39 patients in arm B responded. The difference between these response rates was not statistically significant. As for adverse reactions to the intravesical chemotherapy, local inflammatory symptoms were observed in half of the patients, although no systemic reaction was observed. No significant difference was found between arm A and arm B, except for urinary turbidity. In conclusion, at the dose employed in the present clinical trial, there was no clear enhancement of the effect of ADM combined with VR in patients with superficial bladder cancer. Further clinical studies are required to determine the optimal doses of ADM and VR for their combination in intravesical chemotherapy.

Key words Superficial bladder cancer · Adriamycin · Verapamil

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Introduction

Intravesical instillation of anticancer agents is one of the most effective treatments of superficial bladder cancer. Adriamycin (ADM) is considered to be one of the most suitable agents for intravesical chemotherapy. Nevertheless, the response rate to ADM is about 60%, and resistance of tumor cells to this drug had become a problem.

There have been various hypotheses concerning the mechanism of cancer cells' resistance to anticancer agents, but the one of the most attractive mechanisms is the concept of a cell-membrane transport mechanism, especially with involvement of P-glycoprotein. In addition, it is known that verapamil (VR), a calcium-channel blocker, can enhance the effects of anticancer agents in cells that are otherwise resistant and express an excess of P-glycoprotein [9]. Two ADM-resistant cell lines, i.e., KK47/ADM cells [3] and MGH-U1R cells [4], express excess levels of P-glycoprotein. When these cell lines are exposed to VR concomitantly with ADM, there is partial reversal of the cells' sensitivity to ADM. Moreover, it was reported that the cytotoxic effect of ADM was enhanced when VR was concomitantly applied to cells of the T-24 line, which is not resistant to ADM [8]. On the basis of these results, it was considered that concomitant administration of VR with ADM would enhance the clinical effect of ADM in intravesical chemotherapy for patients with superficial bladder cancer.

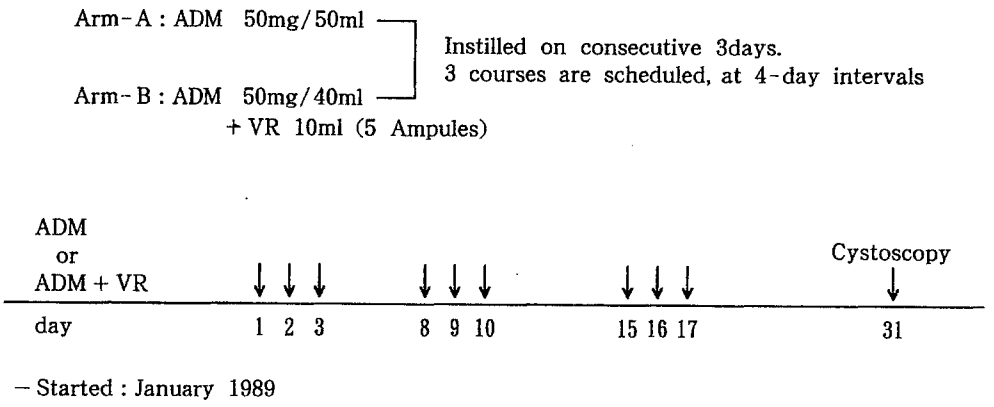

Fig. 1 Treatment schedule used in this study

We carried out the present study to confirm the clinical efficacy and effectiveness of combined intravesical instillation of VR with ADM in the treatment of superficial bladder cancer. This study was designed as a comparative trial of two treatment groups: one group of patients given ADM alone by intravesical instillation and a second group given ADM and VR concomitantly by the same route. An interim report [7] of this study has been issued, and this is the final report.

Patients and methods

Between January 1989 and December 1992, 96 patients with superficial bladder cancer were randomized to receive ADM or ADM plus VR. The eligibility criteria in this clinical trial were the presence of multiple tumors diagnosed as primary bladder cancer on the basis of the clinical or histopathological findings, a pathological stage of Ta or T1, and a histological grade of G1 or G2. It was also necessary that there be no carryover effects of previous therapy. The performance status of the patients had to be between 0 and 3, and it was necessary that the patients have adequate bone marrow, liver, renal, heart, and pulmonary functions. It was also stipulated that it had to be possible to carry out periodic evaluation of the patients by means of cystoscopic examination.

The patients were allocated into one of the treatment arms described below by telephone registration using the minimization method (the balancing factors are initial/recurrent tumors, prior therapy, and institutions). In arm A, 50 mg ADM was dissolved in 50 ml physiological saline (yielding an ADM concentration of 1,000 μg/ml). Similarly, in arm B, 50 mg ADM was dissolved in 40 ml physiological saline, and then 25 mg VR (five ampules of injectable VR; one ampule = 5 mg/2 ml saline) was added to give a total volume of 50 ml (yielding a solution containing ADM at 1,000 μg/ml and VR at 500 μg/ml). The drugs were instilled into the bladder for 3 consecutive days, and three such courses were given with a 4-day interval between each course for a total of nine instillations. And the instilled drug solution was to be retained in the bladder for 2 hours.

At 2 weeks after the final instillation, evaluation of the response was performed on the basis of the findings of cystoscopy (Fig. 1). This evaluation was carried out in accordance with the criteria of the Japanese General Rule for Clinical and Pathological Studies on Bladder Cancer. A complete response (CR) was defined as complete disappearance of the tumor, a partial response (PR) consisted of a reduction of greater than 50% in the size of the tumor, no change (NC) represented a reduction in tumor size of less than 50% or an increase of less than 25%, and progressive disease (PD) was defined as an increase of greater than 25% in the size of the tumor. This study was carried out at two universities, Okayama and Kagoshima, and their affiliated hospitals (Table 1).

Results

During the 4-year period from January 1989 through December 1992, 96 patients were entered into this clinical trial, with 48 being allocated to arm A and 48, to arm B. One patient in arm A (due to a complication of liver cancer) and two patients in arm B (due to G3 disease and cystic cystitis) were ineligible. Three patients were judged to be nonevaluable: one in arm A (due to refusal of the intravesical instillation) and two in arm B (due to failure to visit the hospital and an allocation violation). In addition, six patients in arm A and five in arm B who completed less than six instillations were classified as having been incompletely treated. Finally, 40 patients in arm A and 39 patients in arm B, for a total of 79 patients (representing 82.3% of the registered cases), were considered to have been completely treated (Table 2). The two treatment groups showed

Table 1 Members of the collaborating group

	Director
Okayama University	H. Ohmori
Kagoshima University	Y. Ohi
Tokyo University	Y. Ohashi
Himeji St. Maria Hospital	T. Akagi
Hiroshima Citizens' Hospital	T. Johsen
Imakiire General Hospital	T. Kawabata
Juzen General Hospital	Y. Nasu
Kagawa Prefectural Central Hospital	T. Asahi
Kagoshima Municipal Hospital	N. Sakamoto
Kobayashi Municipal Hospital	I. Yanase
Kobe West City Hospital	Y. Matsumura
Kochi Prefectural Central Hospital	N. Ike
National Ibusuki Hospital	M. Odachi
National Miyakonojo Hospital	T. Kitagawa
Nippon Kokan Fukuyama Hospital	A. Nagai
Ochiai Hospital	S. Yamane
Okayama Central Hospital	T. Kaneshige
Okayama City Hospital	K. Namba
Okayama Red Cross Hospital	K. Kondo
Okayama Saiseikai General Hospital	T. Shiraga
Onomichi City Hospital	A. Mizuno
Oshima Prefectural Hospital	S. Yagi
Shimoinaba Hospital	T. Shimoinaba
So-Gun Medical Association Hospital	M. Masuda
Tottori City Hospital	S. Hayata
Tsuyama Central Hospital	T. Akaeda

Table 2 Patients entered in the study

Regimen	Randomized patients	Ineligible[a]	Nonevaluable[b]	Incomplete[c]	Complete
A	48	1	1	6	40
B	48	2	2	5	39
Totals	96	3	3	11	79

[a] Double cancer, cystitis cystica, grade 3 disease
[b] Dropout in the early period, rejection of intravesical instillation, allocation violation
[c] Fewer than 5 instillations

no significant difference in sex, age, type of disease, tumor morphology, tumor size, number of tumors, stage, or histological grade (Table 3).

Of the 46 evaluable patients in arm A, 12 showed a CR, 16 showed a PR, 13 showed NC, and 5 showed PD, for a response rate (CR+PR) of 60.9%. Similarly, among the 44 evaluable patients in arm B, 8 showed a CR, 13 showed a PR, 21 showed NC, and 2 showed PD, for a response rate of 47.7%. Of the 40 completely treated patients in arm A, 11 showed a CR, 13 showed a PR, 11 showed NC, and 5 showed PD, for a response rate of 60.0%. Among the 39 completely treated patients in arm B, 8 showed a CR, 11 showed a PR, 18 showed NC, and 2 showed PD, for a response rate of 48.7%. These differences in response rates between arm A and arm B were not found to be statistically significant (Table 4).

Table 3 Patients' characteristics

	Eligible patients		≧6 Instillations	
	A (n = 47)	B (n = 46)	A (n = 40)	B (n = 39)
Sex:				
M	38	37	35	31
F	9	9	5	8
Age (years):				
≦49	5	5	5	4
50–59	5	8	4	8
60–69	8	16	8	15
≧70	29	17	23	12
Initial/recurrent disease:				
Initial	17	14	14	13
Recurrent	30	32	26	26
Tumor morphology:				
Pedunculated	24	23	22	18
Broad-based	22	22	17	20
Missing	1	1	1	1
Tumor size:				
<1 cm	34	37	28	30
1–3 cm	10	9	9	9
3–5 cm	3	0	3	0
Number of tumors:				
2–4	31	25	27	21
≧5	15	20	12	17
Almost overall	0	1	0	1
Missing	1	0	1	0
Stage:				
Ta	32	25	27	22
T1	15	18	13	15
Missing	0	3	0	2
Grade:				
G1	25	20	20	16
G2	22	22	20	20
Missing	0	4	0	3

Next, stratified subgroup analysis of the response data was performed according to the patients' background characteristics for those who had completed at least six intravesical instillations. In the initial cases (arm A, 14; arm B, 13), the response rates were 42.9% in arm A and 30.8% in arm B, while among the recurrent cases (arm A, 26; arm B, 26), the response rates were 69.2% and 57.7%, respectively (Table 5). As determined according to tumor morphology, in patients with a pedunculated tuor (arm A, 22; arm B, 18), the response rates were 63.6% in arm A and 61.1% in arm B, whereas among patients with a broad-based tumor (arm A, 17; arm B, 20), the response rates were 58.8% and 35.0%, respectively (Table 6).

As determined with regard to the tumor size, in patients with a tumor measuring less than 1 cm in diameter (arm A, 28; arm B, 30), the response rates were 67.9% in arm A and 56.7% in arm B, whereas among patients bearing a tumor with a diameter of 1 cm or more (arm A, 12; arm B, 9), the response rates were 41.7% and 22.2%, respectively (Table 7). As judged in relation to the number of tumors, of the patients with 2–4 tumors (arm A, 27; arm B, 21), the response rates were 63.0% in arm A and 33.3% in arm B, whereas among patients with 5 or more tumors (arm A, 12; arm B, 18), the response rates were 58.3% and 66.7%, respectively (Table 8). As determined in relation to the pathological stage, in patients with Ta disease (arm A, 27; arm B, 22), the response rates were 66.7% in arm A and 54.6% in arm B, whereas among patients with T1 disease (arm A 13; arm B, 15), the response rates were 46.2% and 40.0%, respectively (Table 9). Finally, as judged according to the grade of disease, in patients with G1 disease (arm A, 20; arm B, 16), the response rates were 65.0% in arm A and 62.5% in arm B, whereas among patients with G2 disease (arm A, 20; arm B, 20), the response rates were 55.0% and 35.0%, respectively (Table 10).

In addition, the patients were divided on the basis of whether they had previously undergone chemotherapy containing an anthracycline anticancer agent. Among the patients who had previously been treated with an anthracycline (arm A, 18; arm B, 17), the response rates were 66.7% in arm A and 52.9% in arm B, whereas in those who had not received an anthracycline anticancer agent (arm A, 22; arm B, 22), the response rates were 54.5% and 45.5%, respectively (Table 11). There was no statistically significant difference in either stratum or in the overall effect determined after adjustment by the Mantel-Henszel test

Table 4 Response rate (*P* Pathological, *C* clinical, *NS* not significant)

Arm	Patients	Response				Response rate	
		CR	PR	NC	PD		
Eligible patients:							
A	46	12 (26.1%) (P-6, C-2)	16 (34.8%)	13 (28.3%)	5 (10.9%)	28 (60.9%)	NS
B	44	8 (18.2%) (P-3, C-0)	13 (29.6%)	21 (47.7%)	2 (4.5%)	21 (47.7%)	
≧6 Instillations:							
A	40	11 (27.5%) (P-5, C-2)	13 (32.5%)	11 (27.5%)	5 (12.5%)	24 (60.0%)	NS
B	39	8 (20.5%) (P-3, C-0)	11 (28.2%)	18 (46.2%)	2 (5.1%)	19 (48.7%)	

Table 5 Response rate of patients who received ≧6 instillations as determined according to type of disease

Arm	Patients	CR+PR		NC+PD
Initial cases:				
A	14	6 (42.9%)	NS	8 (57.1%)
B	13	4 (30.8%)		9 (69.2%)
Recurrent cases:				
A	26	18 (69.2%)	NS	8 (30.8%)
B	26	15 (57.7%)		11 (42.3%)

Table 6 Response rate of patients who received ≧6 instillations as determined according to tumor morphology[a]

Arm	Patients	CR+PR		NC+PD
Pedunculated cases:				
A	22	14 (63.6%)	NS	8 (36.4%)
B	18	11 (61.1%)		7 (38.9%)
Broad-based cases:				
A	17	10 (58.8%)	NS	7 (41.2%)
B	20	7 (35.0%)		13 (65.0%)

[a] Missing = 1

Table 7 Response rate of patients who received ≧6 instillations as determined according to tumor size

Arm	Patients	CR+PR		NC+PD
<1 cm:				
A	28	19 (67.9%)	NS	9 (32.1%)
B	30	17 (56.7%)		13 (43.3%)
≧1 cm:				
A	12	5 (41.7%)	NS	7 (58.3%)
B	9	2 (22.2%)		7 (77.8%)

Table 8 Response rate of patients who received ≧6 instillations as determined according to tumor number[a]

Arm	Patients	CR+PR		NC+PD
2–4:				
A	27	17 (63.0%)	NS	10 (37.0%)
B	21	7 (33.3%)		14 (66.7%)
≧5, almost overall:				
A	12	7 (58.3%)	NS	5 (41.7%)
B	18	12 (66.7%)		6 (33.3%)

[a] Missing = 1

Table 9 Response rate of patients who received ≧6 instillations as determined according to stage[a]

Arm	Patients	CR+PR		NC+PD
Ta:				
A	27	18 (66.7%)	NS	9 (33.3%)
B	22	12 (54.6%)		10 (45.4%)
T1:				
A	13	6 (46.2%)	NS	7 (53.8%)
B	15	6 (40.0%)		9 (60.0%)

[a] Missing = 2

Table 10 Response rate of patients who received ≧6 instillations as determined according to grade[a]

Arm	Patients	CR+PR		NC+PD
G1:				
A	20	13 (65.0%)	NS	7 (35.0%)
B	16	10 (62.5%)		6 (37.5%)
G2:				
A	20	11 (55.0%)	NS	9 (45.0%)
B	20	7 (35.0%)		13 (65.0%)

[a] Missing = 3

Table 11 Response rate of patients who received ≧6 instillations as determined according to previous treatment

Arm	Patients	CR+PR		NC+PD
ADM on:				
A	18	12 (66.7%)	NS	6 (33.3%)
B	17	9 (52.9%)		8 (47.1%)
ADM off:				
A	22	12 (54.5%)	NS	10 (45.5%)
B	22	10 (45.5%)		12 (54.5%)

over strata defined by the above-mentioned background characteristics.

As for adverse reactions to the intravesical chemotherapy, local inflammatory symptoms such as urinary frequency, micturition pain, hematuria, difficulty in urination, and urinary turbidity were recorded by the physicians in charge and are listed in Table 12. Urinary frequency and micturition pain showed a tendency to manifest at a high incidence in arm B. The incidence of urinary turbidity was significantly higher in arm B. However, these adverse reactions were reversible, and they did not represent any special problem. No systemic adverse reaction was observed in either arm A or arm B.

Table 12 Incidence of local adverse reactions to therapy

Side effect	Arm	Severity of reactions[a]				
		–	+	++	+++	Missing
Urinary frequency	A	25 (53.2%)	9 (19.2%)	7 (14.9%)	5 (10.6%)	1 (2.1%)
	B	16 (34.8%)	10 (21.7%)	10 (21.7%)	8 (17.4%)	2 (4.4%)
Micturition pain	A	25 (53.2%)	13 (27.7%)	6 (12.8%)	2 (4.2%)	1 (2.1%)
	B	16 (34.8%)	15 (34.6%)	9 (19.6%)	4 (8.7%)	2 (4.4%)
Hematuria	A	36 (76.6%)	7 (14.9%)	1 (2.1%)	2 (4.3%)	1 (2.1%)
	B	32 (69.6%)	7 (15.2%)	4 (8.7%)	1 (2.2%)	2 (4.4%)
Difficulty in urination	A	42 (89.4%)	2 (4.3%)	0	2 (4.3%)	1 (2.1%)
	B	38 (82.6%)	3 (6.5%)	2 (4.3%)	1 (2.2%)	2 (4.4%)
Urinary turbidity*	A	40 (85.1%)	5 (10.6%)	1 (2.1%)	0	1 (2.1%)
	B	31 (67.4%)	8 (17.4%)	1 (2.2%)	3 (6.5%)	3 (6.5%)

* $P = 0.044$ (Mantel score test)
[a] –, None; +, slight; ++, moderate; +++, severe

Discussion

Various studies have been carried out to date with regard to the expression of P-glycoprotein in bladder cancer. Moriyama et al. [6] demonstrated that P-glycoprotein was expressed in 11 of 31 (35.5%) cases of untreated bladder cancer. Kageyama et al. [2] reported that an overexpression of P-glycoprotein was not detected in six untreated bladder cancer patients but was observed in each of three patients who had been treated previously. In addition, Benson et al. [1] carried out a flow-cytometry study on the expression of P-glycoprotein, and they reported weak expression in 11 patients and strong expression in 3 of 18 patients with untreated bladder cancer. In consideration of these findings, we surmise that expression of P-glycoprotein is weak and low in frequency in untreated cases, whereas it is greatly elevated in cases of previously treated bladder cancer.

Regarding the question of whether verapamil is capable of enhancing the effect of anticancer agents in the treatment of bladder cancer, considerable research has been carried out on cultured ADM-resistant cell lines. Both KK47/ADM cells [3] and MGH-U1R cells [4] are resistant to ADM as a result of having been continuously exposed to the drug, and overexpression of P-glycoprotein has been demonstrated in these cells. The KK47/ADM cells were 271 times more resistant to ADM as compared with the parent cell line KK47. However, when KK47/ADM cells were exposed to ADM with the addition of VR to the culture medium at a level of 10 μg/ml, the 50% growth-inhibitory concentration (IC_{50}) of ADM decreased from 4.6×10^{-1} to 1.6×10^{-2} μg/ml (IC_{50} ratio, 29). Similarly, the MGH-U1R cells were 9 times more resistant to ADM as compared with the parent cell line MGH-U1. Again, the addition of VR to the cultured medium at a level of 16 μg/ml lowered the IC_{50} for ADM from 20 to 8 μg/ml (IC_{50} ratio, 2.5). Thus, as shown by these data, it has been demonstrated that the concomitant use of VR with ADM enhances the cytotoxic effects of ADM against cultured cell lines that are resistant to ADM and overexpress P-glycoprotein. Moreover, it has also been reported that the concomitant use of VR with ADM even enhances the effects of ADM against the T24 cell line which is not an ADM-resistant line [8].

Basic studies have also been carried out on the instillation of verapamil into the bladder. Long et al. [4] instilled [^{3}H]-VR into the bladder of rabbits and then investigated the penetration of this agent into the bladder wall and its transfer to the blood. They found that the [^{3}H]-VR was distributed at a high concentration in the mucosa of the bladder by 1 h after its instillation into the bladder, whereas its concentration in the serosal side was extremely low and almost none of the drug could be detected in the venous blood. Yoshimoto (unpublished data) simultaneously instilled ADM at 2,000 μg/ml and VR at 1,000 μg/ml into the bladder of beagle dogs and examined the effects of these drugs on the bladder mucosa and their absorption via the bladder wall. He observed no significant histopathological change in the bladder mucosa and little absorption into the blood following a 6-h retention of the drugs in the bladder. In addition, when 25 mg VR was delivered into the bladder of two patients with bladder cancer, adverse reactions such as a decrease in blood pressure or local inflammatory symptoms in the bladder, were not seen (Yoshimoto, unpublished data).

On the basis of the evidence described above, we first carried out a pilot study in which ADM and VR were concomitantly given as intravesical instillation chemotherapy to 8 patients with superficial bladder cancer that had recurred in spite of various treatments [10]. Evaluation was impossible in 1 patient due to failure to return to the hospital, but the remaining 7 patients were evaluable. Of the 7 patients evaluated, 1 showed a CR, 5 showed a PR, and 1 showed NC, for a response rate of 85.7%. As for adverse reactions, mild to moderate local inflammatory symptoms were observed in 3 patients (42.9%), but no systemic side effect was observed. These findings were considered to be superior in comparison with the results of a previous study on intravesical instillation of ADM alone at a concentration of 1,000 μg/ml in 28 patients [5], since the response rate in that study had been 32%.

We thus proceeded to carry out the clinical trial reported herein. The objective of this study was to confirm the clinical efficacy and effectiveness of combined intravesical chemotherapy of ADM with VR in the treatment of superficial bladder cancer. The response rates were 60.0% in arm A and 48.7% in arm B, but the difference between these response rates was not statistically significant. In addition, for both of the treatment groups, the response rates were evaluated according to the patients' background characteristics, but no statistically significant difference between arm A and arm B was found after adjustment of any of those characteristics. Moreover, in patients who had undergone previous treatment with an anthracycline anticancer agent, the response rates were 66.7% (12/18) in arm A and 52.9% (9/17) in arm B and, again, the difference was not statistically significant. We also investigated the disease-free period until recurrence after the completion of this intravesical instillation chemotherapy and subsequent surgery, but no statistically significant difference was found between the two treatment groups (log-rank test, data not shown). In addition, after the completion of the present treatment regimens, disease progression was observed in five patients in arm A and three patients in arm B.

As for adverse reactions to the intravesical chemotherapy, local inflammatory symptoms were observed in half of the patients, although no systemic reaction was observed. No significant difference was found between arm A and arm B, except for urinary turbidity.

On the basis of these findings, it can be concluded that there was no clear demonstration of enhancement of the effect of ADM as a result of concomitant administration of VR at the doses employed in the present clinical trial. Further basic and clinical examinations will be necessary to determine the optimal doses and schedule for intravesical chemotherapy with ADM and VR.

References

1. Benson MC, Giella J, Whang IS, Buttyan R, Hensle TW, Karp F, Olsson CA (1991) Flow cytometric determination of the multidrug resistant phenotype in transitional cell cancer of the bladder: Implications and applications. J Urol 146: 982
2. Kageyama Y, Katoh M, Okada K, Yoshida K, Tsuruo T (1991) Detection of P-glycoprotein in human urological carcinomas and its relationship to epidermal growth factor receptor expression. Eur Urol 20: 58
3. Kimiya K, Naito S, Soejima T, Sakamoto N, Kotoh S, Kumazawa J, Tsuruo T (1992) Establishment and characterization of a doxorubicin-resistant human bladder cancer cell line, KK47/ADM. J Urol 148: 441
4. Long JP, Prout GR, Wong YK, Lin C (1990) The effect of verapamil on a multi-drug resistant bladder carcinoma cell line and its potential as an intravesical chemotherapeutic agent. J Urol 143: 1053
5. Matsumura Y, Ozaki Y, Ohmori H, Okayama Urological Cancer Collaborative Group (OUCCG) (1983) Intravesical adriamycin chemotherapy in bladder cancer. Cancer Chemother Pharmacol 11 [Suppl]: S69
6. Moriyama M, Sugawara I, Hamada H, Tsuruo T, Kato T, Sato K, Hikage T, Watanuki T, Mori S (1991) Elevated expression of P-glycoprotein in kidney and urinary bladder cancers. Tohoku J Exp Med 164: 191
7. Ohi Y, Ohmori H, Shirahama T, Kawahara M, Matsumura Y, Tsushima T, Ohashi Y (1992) Intravesical instillation of Adriamycin in the presence or absence of verapamil for the treatment of superficial bladder cancer: preliminary report of a collaborative study. Cancer Chemother Pharmacol 30 [Suppl]: S50
8. Simpson WG, Tseng T, Anderson KC, Harty JI (1984) Verapamil enhancement of chemotherapeutic efficacy in human bladder cancer cells. J Urol 132: 574
9. Tsuruo T (1981) Enhancement of antitumor activity of anticancer drugs by verapamil (in Japanese). Jpn J Cancer Chemother 8: 665
10. Yoshimoto J, Saegusa M, Ochi J, Hara M, Akagi T, Obama T, Matsumura Y, Ohmori H, Tanahashi T (1987) Intravesical chemotherapy of adriamycin and verapamil on the patients with recurrent superficial bladder cancer: perliminary report (in Japanese). Jpn J Cancer Chemother 14: 1950