Cancer Chemother Pharmacol (1995) 35: 357–363

ORIGINAL ARTICLE

Toshiro Kuroiwa · Seiji Naito · Kanehiro Hasuo
Takashi Kishikawa · Kouji Masuda
Jyoichi Kumazawa

Phase II study of a new combined primary chemotherapy regimen, intravenous methotrexate and vincristine and intraarterial Adriamycin and cisplatin, for locally advanced urinary bladder cancer: preliminary results

Received: 7 March 1994/Accepted: 15 July 1994

Abstract A phase II study of a new combination therapy was performed using intraarterial (i.a.) cisplatin and Adriamycin in combination with i.v. methotrexate and vincristine for 27 patients with invasive urinary bladder carcinoma of stages T2–3NOMO, and the therapeutic effects were assessed. Methotrexate (20 mg/m^2) was given i.v. on days 1,15, and 22, and vincristine (0.7 mg/m^2) was injected i.v. on day 2 before i.a. infusion therapy and on days 15 and 22. The i.a. chemotherapy was performed after both superior gluteal arteries had been embolized using 3- or 5-mm stainless-steel coils. A mixture of cisplatin (50–70 mg/m^2) and Adriamycin (20 mg/m^2) was infused i.a. via both internal iliac arteries over a period of 20–30 min. Angiotensin II (mean dose, 21 μg) was simultaneously infused i.a. in 15 of 27 patients. In 24 of the 27 patients, at least 2 cycles of full-dose chemotherapy were completed. The dose was decreased in the remaining 3 patients because of their poor health status and advanced age. Among the 27 patients, 9 and 14 had complete (CR) and partial responses (PR), respectively; 3 manifested no change (NC), and 1 had progressive disease (PD). The objective response rate (CR + PR) was 85.2%. Among the 27 patients staged T2–3 NOMO, 6 (CR, 1; PR, 5) underwent total cystectomies and 18 (CR, 8; PR, 8; NC, 2) had transurethral resection of a bladder tumor (TUR-Bt) or partial resections following chemotherapy. The remaining 3 diminished-dose patients had no surgery. Of the 27 patients, 22 were alive after a median follow-up period of 21 + (range, 7–48 +) months. No significant side effect was observed except for lower extremity paresthesias in 5 patients (18.5%). These results point to the effectiveness of this therapy and to the possibility of urinary bladder preservation in patients with invasive, advanced urinary bladder cancers.

Key words Urinary bladder cancer · Intraarterial infusion · Cisplatin · Adriamycin · Angiotensin II · Interventional procedures

T. Kuroiwa · K. Hasuo · K. Masuda
Department of Radiology, Kyushu University, Fukuoka, Japan

S. Naito · J. Kumazawa
Department of Urology, Kyushu University, Fukuoka, Japan

T. Kishikawa
Department of Radiology, Saga Medical School, Saga, Japan

T. Kuroiwa (✉)
Department of Radiology, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan

Introduction

Systemic chemotherapy regimens for urinary bladder cancer using cisplatin alone [13], CMV (cisplatin, methotrexate, and vinblastine) [9], or M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) therapy [15–17] have reportedly been effective in as many as 50%–70% of patients with primary lesions. M-VAC therapy has recently become a widely used chemotherapy regimen for invasive urinary bladder cancer. However, M-VAC therapy is usually performed i.v. and its complete remission rate is reportedly about 24% [15].

Intraarterial (i.a.) infusion chemotherapy is often superior to i.v. administration because a high concentration of anticancer drugs can be maintained at the tumor site [2]. Local i.a. infusion chemotherapy has been widely prescribed since Klopp et al. [6] reported its efficacy for human head and neck cancer. Cisplatin and Adriamycin are safe and effective anticancer agents in i.a. chemotherapy for the control of primary urinary bladder cancer [10]. On the other hand, vincristine [14] and methotrexate [11] are metabolic anticancer drugs, and there are few reports of their use as i.a. agents because of their toxicity, such as vasculitis or disorders in organic tissues. We therefore designed

a phase II study of a new combination therapy delivered by infusing cisplatin and Adriamycin via both internal iliac arteries in combination with systemic i.v. chemotherapy using methotrexate and vincristine instead of vinblastine [1]. The regimen of this therapy was modified from the original i.v. M-VAC therapy [17].

This new therapy was especially intended to determine the feasibility of enhancing the probability of bladder preservation. Furthermore, in 15 of the 27 patients, angiotensin II (AT-II) was combined in the i.a. infusions to enhance the delivery of the anticancer drugs to the tumor tissue by constricting the vessels supplying the normal tissues, a method using AT-II-induced hypertension chemotherapy that was first reported by Suzuki et al. [19]. We had also observed by animal experimentation that i.a. infusion of cisplatin with AT-II increased the concentration of platinum in tumors as compared with cisplatin administration alone [8]. In the present study, the therapeutic effects of this regimen on invasive urinary bladder cancer were assessed, and the feasibility of preserving the urinary bladder is discussed in this report.

Table 1 Characteristics of the 27 patients studied

Age (years)	35–88 (median, 72)
Sex (M/F)	20/7
Performance status:	
0	23
1	3
2	1
Histology:	
Transitional-cell	26 (G2, 16; G3, 10)
Squamous-cell	1
Clinical staging:	
T2NOMO	5
T3aNOMO	17
T3bNOMO	5

Table 2 Chemotherapeutic agents, doses, and times of administration

Methotrexate	20 mg/m^2	Days 1,15,22	i.v.
Vincristine	0.7 mg/m^2	Days 2,15,22	i.v.
Adriamycin	20 mg/m^2	Day 2	i.a.
Cisplatin	50–70 mg/m^2	Day 2	i.a.

Patients and methods

The criteria for patient eligibility included primary bladder cancer of stages T2–4NOMO, no previous chemotherapy, and no significant disorder of kidney, heart, liver, or bone marrow function. Neither patients with metastatic disease nor those with other active neoplasms were included in this study. Diagnostic and staging procedures were based on cystoscopy, intravesical ultrasonography, excretory urography, chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI), bone scan, transurethral (TU) deep biopsy, bimanual examination using anesthesia, and routine laboratory analyses. The patients studied consisted of 20 men and 7 women who ranged in age from 35 to 88 years (median, 72 years). According to the TNM classification, 5, 17, and 5 cases were classified as stages T2NOMO, T3aNOMO, and T3bNOMO, respectively. The histological diagnoses made by transurethral resection (TUR) or TU biopsy included 26 cases of transitional-cell carcinoma and 1 case of squamous-cell carcinoma (Table 1).

A phase II study of the therapy schedule was performed as follows. Methotrexate (20 mg/m^2) was given i.v. on days 1, 15, and 22, and vincristine (0.7 mg/m^2) was infused i.v. on day 2 before i.a. infusion therapy and on days 15 and 22 (Table 2). The i.a. chemotherapy was performed after bilateral internal iliac angiography on day 2. The right and left superior gluteal arteries were embolized using 3- or 5-mm stainless-steel coils to prevent high concentrations of anticancer drugs from flowing into the gluteal regions. Solutions of cisplatin (50–70 mg/m^2) and Adriamycin (20 mg/m^2) were infused i.a. via both internal iliac arteries over a period of 20–30 min. The doses of cisplatin were considered according to the patients' health status, such as their renal function and age. Concomitantly, AT-II (mean dose, 21 μg) was given during the i.a. infusion therapy to 15 patients without a history of hypertension or any other sign of poor health. In 15 of the 27 patients, AT-II was connected via another route with the solutions of cisplatin and Adriamycin to obviate transient excessively hypertensive states exceeding 200 mmHg or severe headaches (Fig. 1).

All 27 patients completed at least 2 courses of chemotherapy. The number of cycles of chemotherapy was determined according to the patients' clinical tumor responses and physical status. The duration of each course was usually 28 days; the next course of chemotherapy was started within 2 weeks.

The follow-up examinations mentioned above were repeated after the completion of each course of therapy. Evaluation of the therapeutic effects of this regimen was based on the patients' clinical responses. Tumor regression was assessed using CT or MRI at 2 weeks after the completion of the final course of therapy. The greatest diameters of the tumors were measured. The percentages of decrease were determined as follows:

$$\text{Percentage decrease (\%)} = \frac{\text{Diameter before treatment} - \text{Diameter after treatment}}{\text{Diameter before treatment}} \times 100.$$

Antitumor effects were graded according to the criteria for evaluating clinical effects of chemotherapy for solid cancers established by the Japan Society for Cancer Therapy [7]. These criteria are as follows: (1) complete response (CR)—resolution of all measurable, evaluable, and secondary lesions and the absence of new lesions for at least 4 weeks; (2) partial response (PR)—a decrease of 50% or more in the sizes of bidimensionally measurable lesions, a lack of progression of evaluable lesions or secondary lesions due to tumor, and the absence of new lesions for at least 4 weeks; (3) no change (NC)—neither a 50% decrease in bidimensional lesions nor a 30% decrease in unidimensional lesions (the rate of increase of either type of lesion being maintained within 25%), a lack of progression of secondary lesions due to tumor, and the absence of new lesions for at least 4 weeks; and (4) progressive disease (PD)— an increase of 25% or more in the size of measurable lesions or progression of other lesions and the appearance of new lesions.

All 27 patients had TUR biopsies to confirm the presence or absence of residual tumor cells histologically, TUR-Bt, or total cystectomy and underwent follow-up examinations. Pathological responses were mainly used for histological assessment of postoperative downstaging. The criteria for selecting patients for preservation of the urinary bladder were: (1) invasive bladder cancer demonstrating a good response to therapy (PR or CR), (2) residual tumor that could be eradicated by segmental resection or TUR-Bt, (3) cases that were inoperable because of poor physical status, or (4) patients who refused surgery.

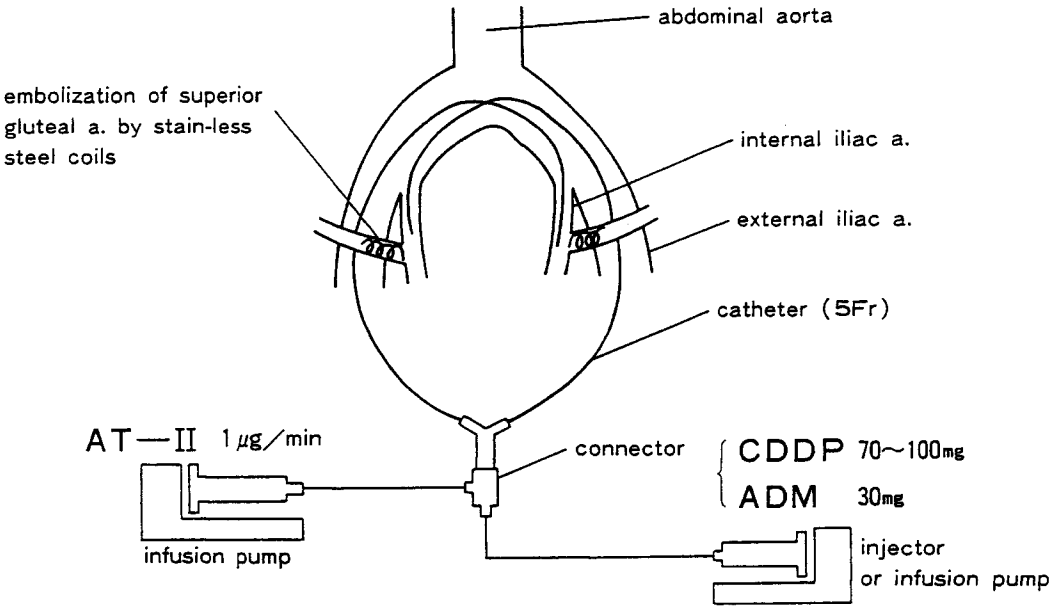

Fig. 1 Schema for i.a. infusion therapy given in combination with AT-II (*a.* Arteries)

Among these 27 patients, side effects such as patient discomfort, myelosuppression, and hepatic or renal dysfunction were observed within several days after the completion of each course of the regimen and were followed further. Our study endpoints were the patients' clinical responses after the final course of chemotherapy and the evaluation of their prognoses.

Results

In all, 2 or more courses of the protocol-based chemotherapy were given to the 27 patients, but the doses were reduced for 3 patients because of complications or the patients' physical status (see Table 6). A mean of 2.4 chemotherapy courses/patient were given (range, 2–4). The embolization of both superior gluteal arteries was successful in all cases. Repeated embolization was unnecessary when two or more courses of i.a. infusion chemotherapy were performed in each case.

Among the 27 patients, a CR was observed in 9; a PR, in 14; NC, in 3; and PD, in 1. The objective response rate (CR + PR) was 85.2% (Table 3). There was no significant difference in the clinically effective rate achieved between the group treated with AT-II (80%) and that treated without AT-II (91.7%), although the rate of the former group was lower than that of the latter. However, the numbers of CRs attained in the former group appeared to be relatively greater than those achieved in the latter.

Among five cases staged T2NOMO (Table 4), a CR was obtained in four. One patient had a PR, but the tumor resolved after TUR-Bt and one additional cycle of this chemotherapy, although this patient eventually died of a different primary tumor, namely, gastric cancer. However, in all five cases of stage T2NOMO disease, the urinary bladders were preserved, and no recurrent tumor was detected (observation period, 14–48 + months).

Table 3 Clinical responses achieved in 27 patients

Clinical responses	AT-II (+)	AT-II (−)	Total
CR	7	2	9
PR	5	9	14
NC	3	0	3
PD	0	1	1
CR + PR	12 (80%)	11 (91.7%)	23 (85.2%)
Totals	15	12	27

Among 22 patients with T3NOMO disease (Tables 5, 6), a CR was obtained in 5 cases, one of which was treated by total cystectomy. Among 13 patients who had a PR, 5 received total cystectomies, 5 underwent TUR-Bt, and 3 had TUR biopsies. Of 3 patients with NC, 1 underwent a segmental resection of the urinary bladder, 1 had a TUR-Bt, and 1 had no surgery.

The observation periods were relatively short; however, 22 of 27 patients in stages T2–3NOMO were alive at a median follow-up period of 21 + months (range, 7–48 + months, Tables 4–6). The 6 patients (CR, 1; PR, 5) whose urinary bladders were removed were alive at a median follow up of 32 + months (range, 11–48 + months). Among the 21 patients whose urinary bladders were preserved, 1 died of a different primary malignancy (PR in T2NOMO, Table 4); 1 died of urinary bladder cancer (PR in T3NOMO, Table 5); and 3, who received diminished doses (stage T3NOMO) because of their poor health status and their advanced age, died within short periods (7–9 months, Table 6). Despite the administration of two

Table 4 Clinical responses and prognoses for 5 patients staged T2NOMO (*malig.* Malignancy)

Patient	Age(years), Sex	Tumor	Courses (*n*)	Responses	Surgery	Outcome
1	35, F	1 × 1 cm, solitary	3	CR	TUR biopsy (no malig.)	Alive (48 + months)
2	78, F	3.3 × 2.1 cm, solitary[a]	3	CR	TU biopsy (no malig.)	Alive (41 + months)
3	65, M	2.5 × 1.8 cm, multiple	2	CR	TUR biopsy (no malig.)	Alive (21 + months)
4	57, M	4 × 3 cm, multiple	2	CR	TU biopsy (no malig.)	Alive (33 + months)
5	73, M	3 × 3 cm, multiple	2	PR (−94%)	TUR-Bt[c] (pT1)	Deceased[b] (14 months)

[a]Squamous-cell carcinoma
[b]Patient died of gastric cancer
[c]*TUR-Bt*, transurethral resection of a bladder tumor

courses of this chemotherapy, among these cases there were neither sufficient therapeutic effects nor long survival periods.

Side effects consisted of clinical symptoms (Table 7) and abnormal laboratory data (Table 8). There were high rates of anorexia and nausea and vomiting, but they were self-limiting. Five patients complained of pain or sensory disturbances in their lower extremities (18.5%), which were severe and persisted for 6 months in one case. Concerning the laboratory data, bone marrow suppression and liver dysfunction were observed in about 80% and 20%–25% of the patients, respectively, but these complications were also transient. No side effect was observed related to AT-II-induced hypertension.

Discussion

Radiation therapy for local tumor control and chemotherapy for systemic disease have been the main forms of neoadjuvant therapy for invasive urinary bladder cancer, but 5-year survival rates of less than 50% have been reported [20]. Some systemic chemotherapy regimens such as cisplatin alone [13], CMV [9], and M-VAC [15–17] have been reported to produce effective rates of about 60% and CR rates of about 20% [15, 16]. We noted the wide use of the M-VAC regimen for the treatment of urinary bladder cancer. To enhance the therapeutic effects, we first designed a new mode of therapy delivery: i.a. infusion chemotherapy using cisplatin and Adriamycin via both internal iliac arteries in combination with systemic chemotherapy using methotrexate and vincristine. We used vincristine instead of vinblastine because the side effect of bone marrow suppression is milder with vincristine than with vinblastine [1, 14]. Hence, i.a. chemotherapy was expected to improve local tumor control as compared with systemic chemotherapy because of the flow of high initial concentrations of anticancer drugs into the tumor tissues with subsequent systemic distribution [2]. In fact, the dose we used for this therapy called for about 70% of that given in the original M-VAC therapy [17] so as to diminish the side effects and to prevent the delay of subsequent surgery.

AT-II was also used in nearly half of the 27 patients with no hypertensive history to enhance drug delivery as well as the chemotherapeutic effects. AT-II, an octapeptide hormone, has a direct vasoconstrictive action, particularly on arterioles of normal tissue, and therefore increases the peripheral resistance and, consequently, the arterial pressure. However, because of the lack of vasoconstrictive action in tumor vessels, the tumor blood flow becomes relatively increased after AT-II administration. Suzuki et al. [19] reported that AT-II-induced hypertension chemotherapy selectively enhanced the delivery of anticancer drugs to tumor tissue. We combined AT-II with i.a. infusions of cisplatin and Adriamycin via both internal iliac arteries in 15 of 27 patients. This enhanced the antitumor effects, with the clinically effective rate (CR + PR) being 80% and the CR rate being relatively high at 46.7% (Table 3). These results were favorable as compared with those mentioned in other treatment reports [3,9,10,13,15,16]. However, there was no significant difference in the clinically effective rate achieved between the groups receiving AT-II and those treated without AT-II, although the CR rate of the former group was somewhat higher than that of the latter. Further examination and follow-up study is necessary after such a limited study of 27 cases.

Total cystectomy was performed in 6 of 22 cases of stage T3NOMO cancers. All 6 patients were alive; 1 had a CR pathologically and 3 had evident downstaging (less than PT1). In another of these 6 patients, tumor cells were not identified in any of the deep muscle layers or in the external bladder walls of the pathological specimens, although the postsurgical stage was pT2pN4 (Table 5). We speculated that the TUR-Bt undertaken prior to total cystectomy was responsible and that the urinary bladder might be preserved in such cases.

Table 5 Clinical responses and prognoses for 19 patients staged T3NOMO (*malig.* Malignancy)

Patient	Age (years), Sex	Tumor	Courses (*n*)	Responses	Surgery	Outcome
1[a]	72, M	7 × 4 cm, multiple	3	CR	Total cystectomy (pT0pNO)	Alive (30 + months)
2	68, M	3.5 × 3 cm, solitary	2	CR	TUR biopsy (No malig.)	Alive (29 + months)
3	75, F	2 × 2 cm, multiple	2	CR	TU biopsy (No malig.)	Alive (17 + months)
4[a]	58, M	6 × 4 cm, multiple	2	CR	TU biopsy (No malig.)	Alive (14 + months)
5	82, M	3 × 3 cm, solitary	2	CR	TUR biopsy (No malig.)	Alive (14 + months)
6	67, M	3.6 × 3.2 cm, solitary	2	PR (− 50%)	Total cystectomy (pT1pNO)	Alive (48 + months)
7	54, M	3.5 × 3.5 cm, solitary	2	PR (− 66%)	Total cystectomy (pT1bpNO)	Alive (32 + months)
8	56, M	3.6 × 1.5 cm, solitary	3	PR (− 98%)	Total cystectomy (pT2pN4)	Alive (32 + months)
9	62, M	4 × 3 cm, multiple	2	PR (− 68%)	Total cystectomy (pT3apNO)	Alive (11 + months)
10	76, M	3 × 2 cm, solitary	2	PR (− 58%)	Total cystectomy (pT2pNO)	Alive (18 + months)
11	88, M	4 × 3 cm, multiple	4	PR (− 69%)	TUR-Bt[b] (pT1)	Alive (26 + months)
12	64, M	4 × 3 cm, multiple	3	PR (− 67%)	TUR-Bt[b] (pTa)	Alive (31 + months)
13[a]	80, M	8 × 6 cm, multiple	3	PR (− 67%)	TUR-Bt[b] (pT1)	Alive (31 + months)
14[a]	79, F	5 × 1.5 cm, solitary	2	PR (− 73%)	TUR-Bt[b] (pT1)	Alive (16 + months)
15	73, M	4 × 2 cm, solitary	2	PR (− 69%)	TUR-Bt[b] (pTa)	Alive (21 + months)
16[a]	47, M	6 × 3 cm, solitary	2	PR (− 58%)	TU biopsy (residual)	Alive (11 + months)
17	73, M	7 × 5 cm, multiple	2	PR (− 89%)	TU biopsy (residual)	Alive (17 + months)
18	68, F	7 × 1 cm, solitary	2	NC (− 43%)	Segmental resection (pT3bpNO)	Alive (36 + months)
19	64, F	5 × 3 cm, solitary	2	NC (+ 7%)	TUR-Bt[b] (pT3, SCC[c])	Deceased (19 months)

[a] T3bNOMO
[b] *TUR-Bt*, transurethral resection of a bladder tumor
[c] *SCC*, squamous-cell carcinoma

The urinary bladder was preserved in 5 cases (CR, 4; PR, 1) staged T2NOMO and in 16 cases (CR, 4; PR, 8; NC, 3; PD, 1) staged T3NOMO. A CR was obtained in 5 patients with T3NOMO disease (Table 5), one of whom received a total cystectomy, which in retrospect might not have been necessary. In all, 22 of 27 patients (81.5%) were alive at a median follow-up of 21 + months (range, 7–48 + months), and 16 of 22 patients (72.7%) were alive with preserved, functional urinary bladders, although the observation period was relatively short. Of the 5 deceased, 3 were diminished-dose T3NOMO-staged patients. Reduction of the therapy dose was necessary in these 3 cases because of their poor clinical status (Table 6) as well as the clinical responses of their tumors and their poor prognoses. It remains debatable as to how we should treat such patients with a poor health status or patients with more advanced stages of cancer. In 1 case, death was due to a different primary malignancy, namely, gastric cancer, and there was no residual tumor in the urinary bladder of this patient (stage T2NOMO, CR). Another patient died of primary urinary bladder cancer, although she had received a full dose of chemotherapy; she showed less of a response (NC) to her therapy, probably

Table 6 Clinical responses and prognoses for 3 dose-limited patients staged T3NOMO[a] (*MTX* Methotrexate, *VCR* Vincristine, *CDDP* Cisplatin, *ADM* Adriamycin)

Patient	Age (years), sex	Tumor	Courses (*n*)	Limited dose	Response	Outcome
1	82, F	5 × 5 cm, solitary	2	MTX 45 mg × 2 VCR 1.5 mg × 2 CDDP 50, 25 mg ADM 20 mg × 2	PR (− 88%)	Deceased (9 months)
2	83, M	6.6 × 10.2 cm, multiple	2	MTX 60, 90 mg VCR 1.5, 3 mg CDDP 30 mg × 2 ADM 20, 30 mg	NC (− 24%)	Deceased (8 months)
3	79, M	6 × 1.5 cm, solitary	2	MTX 60 mg × 2 VCR 1.4, 2.1 mg CDDP 70, 50 mg ADM 30, 20 mg	PD (+ 104%)	Deceased (7 months)

[a]Full-dose chemotherapy was not performed becuase of the patients' poor health status and advanced age

Table 7 Side effects; clinical symptoms and signs of 27 patients[a]

Anorexia	18 (66.7%)
+	14
+ +	4
Nausea & vomiting	10 (37.0%)
+	5
+ +	5
Pain or sensory disturbances of the lower extremities	5 (18.5%)
+	3
+ +	1
+ + +	1
Alopecia	5 (18.5%)
+	3
+ +	2
Stomatitis	2 (7.4%)
+	2
Dyskinesia of fingers	2 (7.4%)
+	2
Atrophy of gluteal muscles	1 (3.7%)
+	1

[a] +, Mild (no medical treatment); + +, moderate (recovered after medical treatment); + + +, severe (chemotherapy stopped due to side effect)

Table 8 Side effects; abnormal laboratory data of 27 patients

Oligochromemia	21 (77.8%)
Grade 1 (Hb, 9.5–10.9 g/dl)	9
Grade 2 (Hb, 9.4–8.0 g/dl)	7
Grade 3 (Hb, 7.9–6.0 g/dl)	5
Leukopenia	18 (66.7%)
Grade 1 (3,000–3,900/mm^3)	5
Grade 2 (2,000–2,900/mm^3)	9
Grade 3 (1,000–1,900/mm^3)	3
Grade 4 (< 900/mm^3)	1
Thrombocytopenia	2 (7.4%)
Grade 1 (9.9–7.0 × 10^4/mm^3)	1
Grade 2 (6.9–5.0 × 10^4/mm^3)	1
GPT elevation	7 (25.9%)
Grade 1 (41–100 IU/l)	6
Grade 2 (100–500 IU/l)	1
GOT elevation	5 (20.8%)
Grade 1 (41–100 IU/l)	4
Grade 2 (100–500 IU/l)	1
BUN elevation	4 (14.8%)
Grade 1 (26–40 mg/dl)	4
Creatinine elevation	1 (3.7%)
Grade 1 (1.6–3.0 mg/dl)	1

because she had squamous-cell carcinoma of the bladder following chemotherapy.

Considering these data, we believe that total cystectomy is not essential for stage T2–3NOMO patients following this new combination therapy and that preservation of the urinary bladder should be a goal in such patients in an attempt to enhance their quality of life. Usually, we would repeat the chemotherapy or perform an additional TUR-Bt or partial resection in case of a local recurrence. Sternberg et al. [18] reported that in 29 of 46 patients staged T2-T4NOMO, bladder preservation was achieved after M-VAC therapy, and 21 of 29 patients (72%) were alive at a median follow-up of 36 + months (range, 11–65 + months). Kaufman et al. [4] stated that 31 of 53 patients (58%) were alive with functional urinary bladders after CMV chemotherapy and radiation therapy (40 Gy) following a median observation period of 48 + months. Our data agreed with these previously reported results. Furthermore, at first we started this regimen as neoadjuvant chemotherapy for preoperative primary bladder cancer. However, as the study progressed and the number of patients who had good responses to this therapy increased, most of the patients complained, refusing total cystectomy and hoping for the preservation of their urinary bladder. This new regimen has recently been accepted as a conservative therapy for the preservation of the urinary bladder in our institutions.

Side effects were not significant except in five patients who complained of pain and/or paresthesia in their lower extremities (Table 7), even though we had embolized both superior gluteal arteries in all cases to prevent gluteal ulceration or damage to the muscles or nerves of both lower extremities, and the toxicity of the

regimen was well tolerated and self limiting. The superior gluteal artery is a major branch of the internal iliac artery, but it does not contribute to the supply of urinary bladder cancers [12]. Neurological side effects may be due to nerve damage induced by vincristine [1,5]. Further examination and analyses are necessary in attempts to diminish side effects. Clinical data (Table 8) indicate that severe renal or liver dysfunction has never occurred with adequate prechemotherapeutic management.

In conclusion, this new combination therapy appears to be clinically safe and effective, especially for T2–3NOMO staged patients. Although the numbers of clinically evaluated cases are small and the observation periods are relatively short, the results obtained in the present study suggest that the urinary bladder can be preserved using this new therapy, even in T2–3NOMO-staged patients with invasive urinary bladder cancer.

Acknowledgements This was a collaborative study performed in the following institutions: Kyushu Kosei Nenkin Hospital, Fukuoka Medical Center Hospital, Sanshinkai Hara Hospital, Kitakyushu City Medical Center, Fukuoka Red Cross Hospital, National Beppu Hospital, Hamanomachi Hospital, Shinkokura Hospital, National Nakatsu Hospital, Saiseikai Yahata Hospital, Kyushu Central Hospital, and Miyazaki Medical College Hospital. We thank the many physicians working in the departments of radiology, urology, and pathology of the above mentioned hospitals.

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