The novel bladder preservation therapy BOAI-CDDP-radiation (OMC-regimen): A new treatment option for invasive bladder cancer patients with lymph node metastasis

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Abstract. We have developed a novel bladder preservation therapy for patients with muscle-invasive bladder cancer and lymph node metastasis: balloon-occluded arterial infusion (BOAI) of cisplatin/gemcitabine, with concomitant hemodialysis and irradiation [the so-called 'OMC (Osaka Medical College) regimen']. The OMC regimen delivers an extremely high concentration of anticancer agent to the site of the tumor, as well as the pelvic area, without causing any adverse systemic effects. In this study, we investigated the efficiency of the OMC regimen in 34 patients who underwent BOAI with cisplatin (100, 200 or 300 mg) along with 60 Gy of irradiation; patients who failed to achieve CR underwent secondary BOAI with gemcitabine (1,600 mg). The overall clinical response was 73.5% (CR: 35.3%; PR: 17.6%; SD: 20.6%). The 5-year overall and progression-free survival rates were 54.4% and 52.5%, respectively. For treatment failure, N2 stage was selected as a significant risk factor by simple and multiple logistic regression analyses. Cox proportional hazards analyses showed that N2 stage, T4 stage and the presence of hydronephrosis were significant risk factors for overall survival. Indeed, 55.6% of patients with N1 stage achieved a complete response (CR) (vs. 12.5% for N2 patients, p=0.0151), and 90% (9/10) of the CR patients survived without recurrence with an intact bladder after a mean follow-up of 85 (range 7-193) weeks. The 3-year progrssion-free survival rate with an intact bladder was 65.8% (vs. 37.5% for N2, p=0.034), and the 5-year overall survival rate was 71.8% (vs. 30.6% for N2, p=0.004). No patients suffered severe toxicities of Grade II or more; the oldest patient, aged 85 years, successfully completed this therapy. In conclusion, the OMC regimen can be regarded as a new option for patients with macroscopic lymph node involvement, especially those at stage N1. Therapy will improve the feasibility of radical cure even without the need for cystectomy in patients for whom surgery after neoadjuvant chemotherapy would otherwise be necessary, and also facilitate potential cure in patients for whom, otherwise, merely palliative treatment would seem the only option.

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Abbreviations: ANC, absolute neutrophil count; BOAI, balloon-occluded arterial infusion; CTCAE, common terminology criteria for adverse events; DSA, digital subtraction angiography; ECOG, eastern cooperative oncology group; HD, hemodialysis; Qu, quartile; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma

Key words: balloon-occluded-arterial-infusion, hemodialysis, invasive bladder cancer, trimodality therapy, lymph node metastasis

Introduction

The prognosis of patients with bladder cancer and macroscopic lymph node metastasis is poor (1-4). Even if down-staging is achieved with neoadjuvant chemotherapy, surgery yields no marked benefit, even for total cystectomy with extended lymph node dissection. No randomized studies have investigated the management of nodal metastasis in such patients, and there is no established curative treatment.

We have developed a novel bladder preservation therapy [referred to hereafter as the 'OMC (Osaka Medical College) regimen'] involving balloon-occluded arterial infusion (BOAI) of an anticancer agent and concurrent hemodialysis (HD) (5-10). This allows the anticancer agent to accumulate at a high concentration at the site of the tumor while ensuring that the systemic concentration remains low, and simultaneous radiation therapy is applied. We have previously reported that >90% of patients with locally advanced urothelial bladder cancer achieved CR, of whom 97% (68/70) did not develop recurrent disease or metastasis within a mean follow-up period of more than 3 years [range, 11-805 weeks; 1st to 3rd quartile (Qu) = 66 to 195] after completion of this therapy (6).

In the present study, we investigated the effectiveness of the OMC regimen for patients with advanced urothelial bladder cancer and macroscopic lymph node metastasis diagnosed by imaging studies. We found that more than 55% of patients with macroscopic lymph node involvement at stage N1 achieved CR (vs. 12.5% for stage N2, p=0.0151), of whom 90% (9/10) did not develop recurrent disease or other metastasis within a mean follow-up period of 85 weeks [range, 7-193 weeks; 1st to 3rd quartile (Qu) =40 to 130] after completion of this therapy. Thus, the OMC regimen can be a new therapeutic option for patients with urothelial bladder cancer and lymph node metastasis, for which no other alternative established treatments are currently available.

Patients and methods

Eligibility criteria. Eligible patients had histologically confirmed muscle-invasive urothelial cancer with lymph node metastasis diagnosed by imaging studies but no other distant metastasis. Imaging studies, including chest computed tomography (CT) scan, abdominal/pelvic magnetic resonance imaging (MRI) and CT scan, and bone scintigraphy were performed before the start of therapy. For clinical staging, we used a simplified form of the 2002 TNM classification to stage bladder tumors (11). All patients who received the OMC regimen had an absolute neutrophil count (ANC) of 1,500 μl, platelet count 100,000 μl, creatinine 3.0 mg/dl, a bilirubin level 3 times the institutional upper limit of the normal range, an AST level 4 times the institutional upper limit of the normal range, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and no prior radiotherapy or systemic therapy for bladder cancer. The study was reviewed and approved by the institutional review board of Osaka Medical College. Patients were informed of the investigational nature of the study and provided written informed consent before study enrollment.

Assessability, toxicity and response criteria. Pretreatment evaluation included a complete history and physical examination, performance status assessment, complete differential blood cell count, electrolytes, blood urea nitrogen, serum creatinine, liver function parameters and appropriate imaging studies to assess the extent of disease. During treatment, patients were seen weekly at our department, when their weight was recorded and toxicity was monitored using the National Cancer Institute's Common Terminology Criteria for adverse events v4.0 (CTCAE). At 6 weeks, patients underwent repeat transurethral resection of the site of the original tumor, ultrasound-guided whole-layer biopsy, and urine cytology, as well as MRI and CT scan of the pelvis, and were evaluated for their response to this therapy. CR was defined as complete disappearance of all measurable and evaluable disease. Duration of response was defined as the period from documentation of the response until evidence of disease recurrence. Survival was the period from study entry until patient death. Patients who achieved CR were observed using our follow-up protocol. However, any evidence of residual tumor was deemed as treatment failure, and such patients underwent secondary BOAI with a higher dosage of cisplatin or gemcitabine (1600 mg), as a salvage therapy. Patients who were found to have only a superficial amount of remaining tumor underwent intravesical injection of Bacillus Calmette Guerin (BCG).

Table I. Patient characteristics.

Characteristic	Patients		
	No.	%	95% CI
Age (years)			
Mean (range)		66 (38-85)	
Gender			
Male	22	64.7	46.5-80.3
Female	12	35.3	19.7-53.5
T stage			
T2	6	17.6	6.76-34.5
T3	11	32.4	17.4-50.5
T4	17	50.0	32.4-67.6
N stage			
N1	18	52.9	35.1-70.2
N2	16	47.1	29.8-64.9
Tumor size			
<3 cm	11	32.4	17.4-50.5
3-5 cm	13	38.2	22.2-56.4
>5 cm	10	29.4	15.1-47.5
Hydronephrosis			
(+)	17	50.0	32.4-67.6
(-)	17	50.0	32.4-67.6
Complete TURBT			
(+)	11	32.4	17.4-50.5
(-)	23	67.6	49.5-82.6
Histology			
UC	30	88.2	72.5-96.7
Non-UC	3	8.82	1.86-23.7
ECOG performance status			
0	21	61.8	43.6-77.8
1	8	23.5	10.7-41.2
2	4	11.8	3.30-27.5
3	1	2.94	0.07-15.3

Follow-up. All patients were followed up on the basis of monthly urine cytology, together with cystoscopy, biopsy and imaging studies, every three months for 2 years, including chest CT scan, abdominal/pelvic MRI and CT scan, and bone scintigraphy, and then at 6-month intervals thereafter.

Statistics. The simple as well as multiple logistic regression analyses were conducted to evaluate the significance of the following variables as risk factors of treatment failure: age, gender, tumor stage, lymph node status, tumor size, hydronephrosis due to tumors, significance of complete resection of tumor, and histology. The life table probabilities of overall survival and progression-free survival were determined using

Table II. Criteria for the administration of cisplatin.

Patients	Dose	Criteria
In the initially enrolled 5 patients		
	100 mg	Renal function (sCr ≥1.3) or age (≥75 years)
	200 mg	Renal function (sCr <1.3) with [age (60-74 years) and T stage (T2 or T3)]
	300 mg	Renal function (sCr <1.3) with [age (<60 years) or T stage: T4]
In the latest 27 patients		
	100 mg	All patients

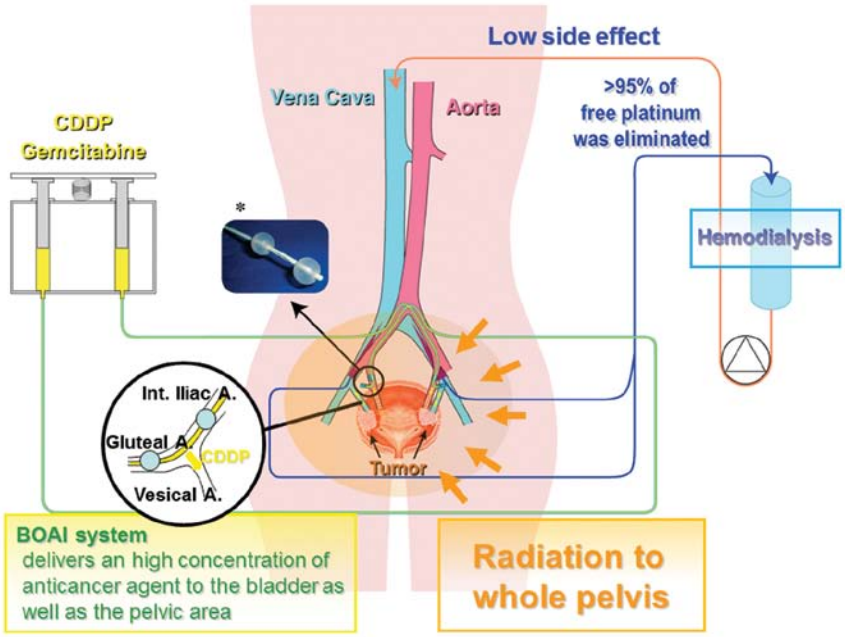

Figure 1. Schema of the OMC regimen (HD-BOAI-CDDP/gemcitabine with radiation). The extracorporeal circuit allowed balloon-occluded intra-arterial infusion of CDDP/gemcitabine concurrent with HD. Through the femoral arterial approach, an intra-arterial catheter equipped with two occlusion balloons was introduced into the posterior trunk of the internal iliac artery on each side. Both the distal and proximal balloons were inflated and immobilized at a position allowing the 'vesical arteries' to be isolated between the balloons. The panel marked with an asterisk shows a image of the intra-arterial catheter (M6F-28-70-TBSB4-ST, Clinical Supply), which is made of polyethylene, 6 French in size, and equipped with two occlusion balloons separated by a distance of 40 mm.

Kaplan-Meier analysis and log-rank test. The Cox proportional hazards analyses was conducted to assess the associations of each factor as described above. Differences at $p<0.05$ were considered to be statistically significant.

Results

Patient characteristics. Between 1997 and 2014, 34 patients (22 males and 12 females) with macroscopic lymph node metastasis diagnosed by imaging studies were treated with the OMC regimen. The characteristics of the patients are shown in Table I.

Treatment details. Patients assigned to the OMC-regimen underwent transurethral resection of the bladder tumor (TURBT) to establish the diagnosis. They were then scheduled to receive the OMC regimen 4-5 weeks after TURBT to allow adequate healing. We administered 100, 200 or 300 mg of cisplatin as a single bolus according to the criteria described in Table II.

For the intra-arterial infusion procedure, we used an intra-arterial catheter equipped with two occlusion balloons (size: 6 Fr., M6F-28-70-TBSB4-ST, Clinical Supply, Tokyo, Japan). The catheter was introduced into the posterior trunk of the internal iliac artery through the femoral arterial approach, and after the distal balloon had passed through the furcation of the anterior trunk of the internal iliac artery, both the distal and proximal balloons were inflated and immobilized, so that the anterior trunk of the internal iliac artery, which lies upstream of the target vessels (the 'vesical arteries') was isolated between the balloons. At this time, using digital subtraction angiography (DSA), it was confirmed that the injected agent did not enter the superior gluteal artery and that there was no back-flow into the internal iliac artery, while the tumor was markedly stained due to active flow of injected contrast medium into the urinary bladder. Fig. 1 illustrates the

Table III. Response and current outcome.

Characteristics	CR			PR			SD			PD		
	No.	%	95%-CI	No.	%	95%-CI	No.	%	95%-CI	No.	%	95%-CI
Total number of patients	12	35.3	19.7-53.5	6	17.6	6.76-34.5	7	20.6	8.70-37.9	9	26.5	12.9-44.4
Duration of response (weeks)												
Mean (range)		99, 7-307 weeks			48, 4-151 weeks			59, 13-171 weeks			0 weeks	
1st, 3rd QU		47, 136 weeks			15, 58 weeks			19, 80 weeks			0 weeks	
Recurrence	1	8.33	0.21-38.5	0	0	0-45.9	4	57.1	18.4-90.1			
Death	1	8.33	0.21-38.5	0	0	0-45.9	3	42.9	9.90-81.6	7	77.8	40.0-97.2
Age (years) mean (range)		58 (38-85)			69 (60-75)			71 (60-85)			68 (55-81)	
Gender												
Male	8	66.7	34.9-90.1	4	66.7	22.3-95.7	3	42.9	9.90-81.6	6	66.7	30.0-92.5
Female	4	40.0	33.3-65.1	2	33.3	4.33-77.7	4	57.1	18.4-90.1	3	33.3	7.49-70.1
T stage												
2	4	33.3	33.3-65.1	2	33.3	4.33-77.7	0	0	0-41.0	0	0	0-33.6
3	4	33.3	33.3-65.1	1	16.7	0.42-64.1	2	28.6	3.67-71.0	4	44.4	13.7-78.8
4	4	33.3	33.3-65.1	3	50.0	11.8-88.2	5	71.4	29.0-96.3	5	55.6	21.2-86.3
N stage												
1	10	83.3	51.6-97.9	3	50.0	11.8-88.2	3	42.9	9.90-81.6	2	22.2	2.81-60.0
2-3	2	16.7	2.09-48.4	3	50.0	11.8-88.2	4	57.1	18.4-90.1	7	77.8	40.0-97.2
Tumor size												
<3 cm	4	33.3	33.3-65.1	1	16.7	0.42-64.1	3	42.9	9.90-81.6	3	33.3	7.49-70.1
3-5 cm	3	25.0	5.49-57.2	2	33.3	4.33-77.7	3	42.9	9.90-81.6	5	55.6	21.2-86.3
>5 cm	5	41.7	15.2-72.3	3	50.0	11.8-88.2	1	14.3	0.36-57.9	1	11.1	0.28-48.2
Hydro												
(+)	5	41.7	15.2-72.3	4	66.7	9.43-99.2	4	57.1	18.4-90.1	4	44.4	13.7-78.8
(-)	7	58.3	27.7-84.8	2	33.3	4.33-77.7	3	42.9	9.90-81.6	5	55.6	21.2-86.3
Comp-TUR												
(+)	5	41.7	15.2-72.3	5	83.3	35.9-99.6	1	14.3	0.36-57.9	0	0	0-33.6
(-)	7	58.3	27.7-84.8	1	16.7	0.42-64.1	6	85.7	42.1-99.6	9	100	66.4-100
Histology												
UC	12	100	73.5-100	6	100	54.1-100	4	57.1	18.4-90.1	8	88.9	51.8-99.7
Non-UC	0	0	0-26.4	0	0	0-45.9	3	42.9	9.90-81.6	1	11.1	0.28-48.2

Hydro, hydronephrosis; Comp-TUR, complete TURBT.

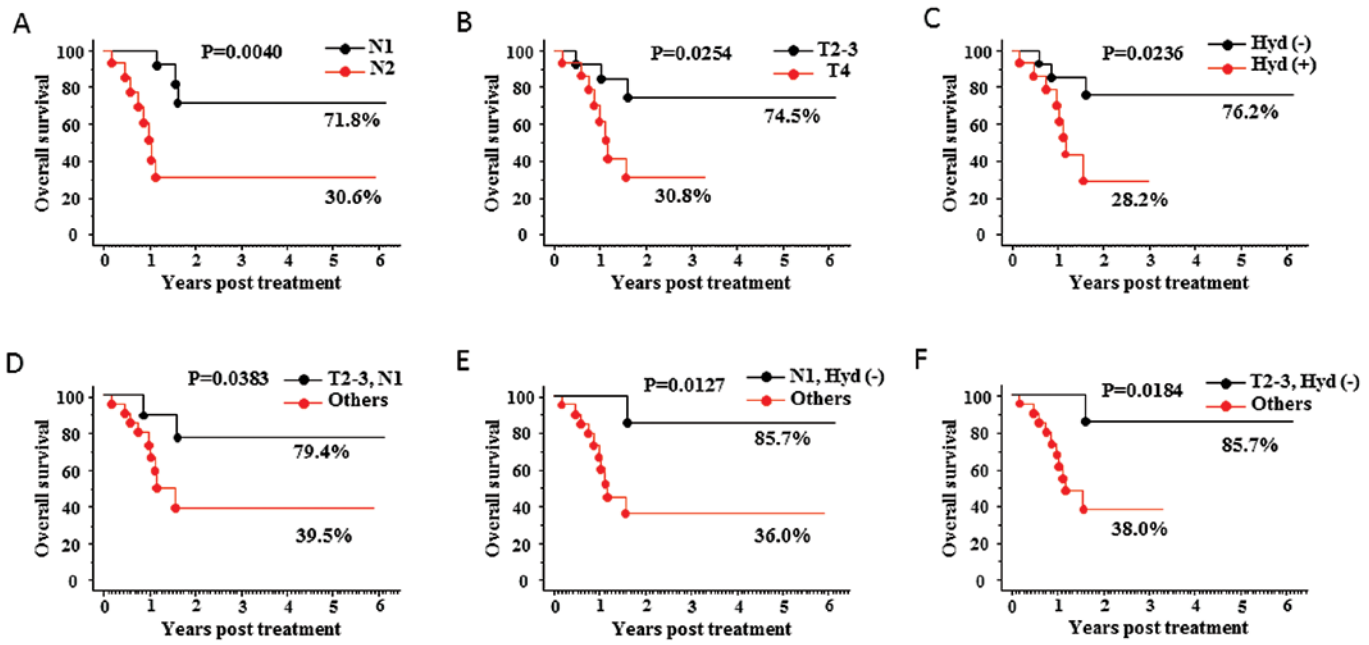

Figure 2. Kaplan-Meier curves for overall survival. The patients were divided into two groups according to lymph node status (N1 vs. N2), T stage (T2-3 vs. T4), and presence or absence of hydronephrosis. Kaplan-Meier curves for overall survival in each group are shown in graphs (A), (B), and (C), respectively. Pairs comprising various combinations of the two sets of criteria were examined: N1 stage with T2-3 stage, N1 stage with absence of hydronephrosis, and T2-3 stage with absence of hydronephrosis. Kaplan-Meier curves of overall survival for each of these pairs are shown in graphs (D), (E), and (F), respectively.

extracorporeal circuit used in the treatment. Various amounts of cisplatin (100, 200 or 300 mg) were locally infused through the catheter over a one-hour period (Table II). Simultaneously, HD was performed via two double-lumen catheters (size: 12 Fr., Argyle®, Tyco Healthcare, Tokyo, Japan) placed in the bilateral common iliac veins for 2 h after the start of arterial infusion. The catheters were connected to a hollow-fiber dialyzer (APS150, Asahi, Tokyo, Japan) with a membrane area of 1.0-1.5 m^2 according to the weight of each patient. The blood flow rate was 180-250 ml/min and the hemodialysis-fluid flow rate was 500 ml/min.

Radiation therapy was administered to the whole pelvis using a CT-planned three-dimensional conformal technique to a total of 60 Gy: 50 Gy (2 Gy/day x25 days) followed by 10 Gy (2 Gy/day x5 days) of local irradiation to the bladder. Patients were treated with the bladder empty. The planned target volume for the bladder included the gross target volume (bladder plus any extravesical tumor) with a 1-cm expansion. At 6 weeks, patients underwent repeat transurethral resection of the site of the original tumor, ultrasound-guided whole-layer biopsy, and urine cytology, as well as MRI and CT scan of the pelvis, and the response to this therapy was then evaluated.

Response. Table III summarizes the treatment response, duration of response, and patient characteristics, including gender, age, T stage, N stage, tumor size, involvement of hydronephrosis, success or failure of complete resection of tumor, and histology. Overall response rate was 73.5% (CR: 35.3%; PR: 17.6%; SD: 20.6%), and 58.8% of the patients survived without recurrence after a mean follow-up period of 82 weeks. The simple as well as multiple logistic regression analyses revealed that lymph node status of N2 stage is the significant risk factor for treatment failure (simple logistic regression analyses: p=0.0151 vs. N1; multiple logistic regression analyses: p=0.0477) (Table IV). The 55% (55.6%, 95% CI, 41.3-89.0%) of patients with lymph node status of N1 stage achieved a complete response as defined by the absence of persistent disease revealed by cystoscopy, biopsy, and urine cytology after therapy (Table III). The 90% of patients with CR were able to retain their urinary bladder with no evidence of recurrent disease or distant metastasis within a mean follow-up period of 85 weeks (range, 7-193 weeks; 1st to 3rd Qu = 40 to 130) from the completion of therapy. In contrast, induction rates of CR was significantly lower in patients with N2 stage (12.5%, p=0.0151 vs. N1).

Survival

Overall survival. The OMC-regimen yielded good outcomes in overall survival for patients with lymph node metastasis with 5-year survival rates of 54.4%. We investigated the significance of each factor, including N stage, T stage, involvement of hydronephrosis, tumor size, tumor number, sex, age, tumor pathology (non-UC vs. UC), and success or failure of complete TURBT as a predictor of overall survival and progression-free survival using the Cox proportional hazards analyses. As shown in Table V, N2 stage, T4 stage, and the presence of hydronephrosis have been selected as the significant risk factors affecting overall survival. The Kaplan-Meier analyses supported the above data as shown in Fig. 2. The 5-year overall survival rates in patients with lymph node status of N1 stage was 71.8% (vs. 30.6% in N2, p=0.0040; Fig. 2A). Those with tumor of T2-3 stage and those without presence of hydronephrosis were 74.5% (vs. 30.8% in T4, p=0.0254; Fig. 2B) and 76.2% (vs. 28.2% in hydronephrosis existed, p=0.0236; Fig. 2C), respectively. Moreover, pairs comprising one each of

Table IV. Risk factors for treatment failure selected by logistic regression analyses.

		Simple		Multiple	
Variables	Category	Odds ratio	p-value	Odds ratio	p-value
N-Stage	N1 vs. N2	8.772	0.0151	8.333	0.0477
T-Stage (T4)	T<4 vs. T4	2.890	0.1574	1.749	0.5772
hydronephrosis	(+) vs. (-)	1.681	0.4745	1.449	0.7431
Tumor size	Cont. variable	1.004	0.8769	1.014	0.7852
Tumor number	Cont. variable	1.147	0.5308	1.136	0.7561
Histology	UC vs. non-UC	1.923	0.6842	2.187	0.6532
Complete TUR	Yes vs. No	1.905	0.3942	3.412	0.2149
Gender	Male vs. Female	2.077	0.3581	3.280	0.3240
Age	Cont. variable	1.146	0.6735	1.976	0.3876

Cont. variable, continuous variable; NV, no value.

Table V. Predictors of overall survival and progression-free survival for the treatment of OMC-regimen evaluated by Cox proportional hazards analyses.

		Overall survival		Progression free survival	
Variables	Category	Odds ratio	p-value	Odds ratio	p-value
N-Stage	N1 vs. N2	5.848	0.0102	5.184	0.0477
T-Stage (T4)	T<4 vs. T4	4.132	0.0384	2.024	0.2077
hydronephrosis	(+) vs. (-)	4.274	0.0359	1.996	0.4816
Tumor size	Cont. variable	1.024	0.8770	1.467	0.4584
Tumor number	Cont. variable	1.042	0.8870	1.217	0.4072
Histology	UC vs. non-UC	1.768	0.4668	1.405	0.6568
Complete TUR	Yes vs. No	4.599	0.1461	7.317	0.0557
Gender	Male vs. Female	1.093	0.8878	1.047	0.9345
Age	Cont. variable	1.009	0.7198	1.015	0.4632

Cont. variable, continuous variable; NV, no value.

the two sets of criteria were examined as follows: N1 stage with T2-3 stage, N1 stage with absence of hydronephrosis, and T2-3 stage with absence of hydronephrosis. Indeed, the 5-year overall survival rates in patients with N1 stage with T2-3 stage, those with N1 stage with absence of hydronephrosis, and those with T2-3 stage with absence of hydronephrosis were 79.4% (vs. 39.5% in others, p=0.0383; Fig. 2D), 85.7% (vs. 36.0% in others, p=0.0127; Fig. 2E), and 85.7% (vs. 38.0% in others, p=0.0184; Fig. 2F), respectively.

Progresion-free survival. The OMC-regimen also yielded good outcomes in progression-free survival for patients with lymph node metastasis with 5-year survival rates of 52.5%. More than 50% of patients with lymph node metastasis survive with their functioning bladder at 5-years after the treatment; this is the most important issue for the bladder preservation therapy. As for the risk factors, Cox proportional hazards analyses selected N2 stage as a significant risk factor affecting progression-free survival (Table V). Kaplan-Meier analyses supported the above data as shown in Fig. 3. The 5-year progression-free survival rate for patients with N1 lymph node status was 65.8% (vs. 37.5% for those with N2 stage, p=0.0340; Fig. 3A). Moreover, pairs comprising various combinations of the two sets of criteria were examined: N1 stage with T2-3 stage, N1 stage with absence of hydronephrosis, and T2-3 stage with absence of hydronephrosis. The 3-year progression-free survival rate for patients with N1 stage with T2-3 stage and those with N1 stage with absence of hydronephrosis, was 71.2% (vs. 39.1% for others, p=0.0495; Fig. 3D) and 79.5% (vs. 35.6% for others, p=0.0394; Fig. 3E), respectively.

Toxicity. One of the most significant outcomes of the OMC regimen was that its related toxicities were markedly less severe than those reported for other protocols, as shown in Table VI. None of the patients suffered Grade II or more severe toxicities. Six patients [17.6%, 95% confidence interval (CI), 6.76-34.5%] experienced Grade I blood/bone-marrow toxicity, 13 (38.2%, 95% CI, 22.2-56.4%) had gastrointestinal toxicity, and 1 (2.94%, 95% CI, 0.07-15.3%) had neuropathy.

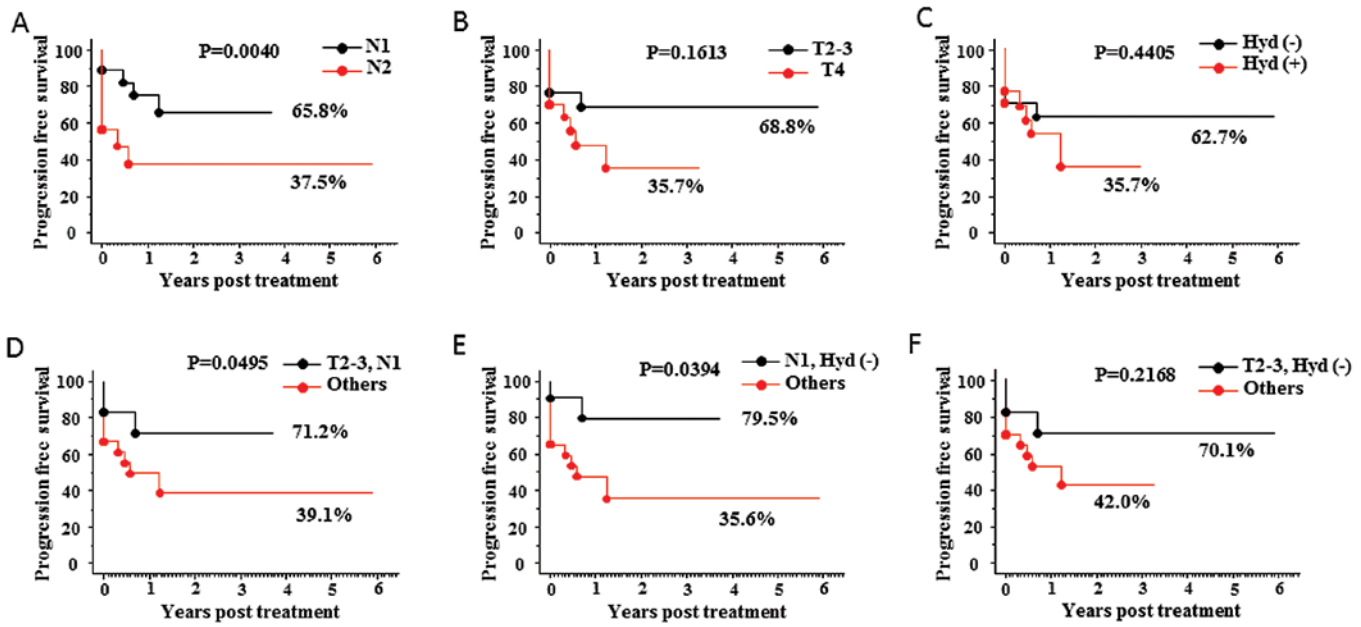

Figure 3. Kaplan-Meier curves for progression-free survival. The patients were divided into two groups according to lymph node status (N1 vs. N2), T stage (T1-3 vs. T4), and presence or absence of hydronephrosis. Graphs (A), (B), and (C), respectively, show Kaplan-Meier curves of progression-free survival in each group. Pairs comprising one each of the two sets of criteria were examined as follows: N1 stage with T2-3 stage, N1 stage with absence of hydronephrosis, and T2-3 stage with absence of hydronephrosis. Kaplan-Meier curves of progression-free survival for each of these pairs are shown in graphs (D), (E), and (F), respectively.

Table VI. Toxicity.

	Grade			Duration		
Toxicity	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3-4 No. (%)	<3 Days No. (%)	3-7 Days No. (%)	>7 Days No. (%)
Blood/bone marrow						
Total	6 (17.6)	0	0	0	6 (17.6)	0
Granulocytopenia	6 (17.6)	0	0	0	6 (17.6)	0
Anemia	4 (11.8)	0	0	0	4 (11.8)	0
Gastrointestinal						
Total	13 (38.2)	0	0	7 (20.6)	6 (17.6)	0
Anorexia	11 (32.4)	0	0	8 (23.5)	3 (8.82)	0
Constipation	3 (8.82)	0	0	2 (5.88)	1 (2.94)	0
Diarrhea	6 (17.6)	0	0	3 (8.82)	3 (8.82)	0
Nausea	10 (29.4)	0	0	5 (14.7)	5 (14.7)	0
Vomiting	3 (8.82)	0	0	1 (2.94)	2 (5.88)	0
Neuropathy	1 (2.94)	0	0	0	0	1 (2.94)

The duration of blood/bone-marrow toxicity, including granulocytopenia and anemia, was relatively short: median duration was 5 days for granulocytopenia (range, 3-7 days) and 5 days for anemia (range, 3-5 days). No patients received granulocyte colony-stimulating factor or transfusion of red blood cells. Gastrointestinal toxicity included anorexia in 11 patients, constipation in 3, diarrhea in 6, nausea in 10, and vomiting in 3, but all symptoms disappeared within 5 days after intra-arterial infusion. One patient experienced Grade I neuropathy in the peroneal nerve area, but disappeared by the 12 months after the treatment. There were no other adverse reactions such as renal failure, genitourinary toxicity, or life-threatening complications.

Discussion

The present study showed that the OMC regimen is a new therapeutic option for patients with advanced urothelial bladder cancer and pelvic lymph node metastasis diagnosed by imaging studies. New anticancer agents such as gemcitabine and/or taxane-based agents have improved the outcome of muscle-invasive bladder cancer. However, most patients with lymph

node involvement still have a poor prognosis: the 5-year overall survival rates for patients with lymph node metastasis at stage N1, N2, or N3 are ~40, 20, and <10%, respectively (1-4), despite total cystectomy after down-staging achieved by neoadjuvant chemotherapy. No randomized studies have investigated the management of nodal metastasis, and there is no established curative treatment for such patients. Many studies have shown that involvement of pelvic lymph nodes is the strongest independent predictor of disease-specific mortality in patients with bladder cancer (1,12-14). The number of lymph nodes involved (2,15,16), and/or lymph node density (number of positive nodes per total number of nodes removed), as proposed previously are significant prognostic factors (17-20). Extended nodal dissection, which may eradicate a greater number of involved lymph nodes, has been reported to contribute not only to accurate evaluation of pathological nodal status but also to improvement of prognosis (21-24). Moreover, neoadjuvant chemotherapy may also help to control lymph node involvement (25-28).

In our previous study, we found that the OMC regimen achieved significantly better outcomes in patients with organ-confined muscle-invasive bladder cancer than in those who underwent total cystectomy. More than 90% of patients achieved CR, and most of the patients survived without recurrence, with a 10-year bladder-intact survival rate of >80% (6). This may also have been attributable to control of lymph node involvement. The high concentration of anticancer agent, together with irradiation, would likely be responsible for the better outcomes achieved with the OMC regimen than with cystectomy.

The results of the present study would appear to reflect the above situation. The overall response rate was 73.5% (CR: 35.3%; PR: 17.6%; SD: 20.6%), for patients with macroscopic lymph node involvement, and more than 50% of those patients (54.2%) survived without recurrence 5 years after the treatment. This suggests that the present treatment would be a useful alternative for improving the survival of patients with advanced bladder cancer and lymph node involvement.

Our investigation of the risk factors for treatment failure and patient survival revealed that lymph node status was the one of the most significant. Indeed, 55.6% of patients with N1 stage disease achieved a complete response (CR), and 90% of the CR patients survived without recurrence with an intact bladder after a mean follow-up of 85 weeks. These results emphasize the importance of nodal control for the treatment of advanced bladder cancer. Moreover, it may be possible to state that the OMC regimen can even be considered as a curative treatment for patients at stage N1.

The mechanism by which BOAI exerts its anticancer effect is considered to be delivery of an extremely high concentration of anticancer agent to the tumor site, as well as to the pelvic lymph nodes. Collins (29) compared plain intravenous infusion and plain intra-arterial infusion of the same dose of cisplatin and reported that the intratumoral Pt concentration was 1.4-5.0 times higher after the latter than after the former. Mitsuzane *et al* (30) reported that if the tumor-feeding artery was occluded by a balloon, >6 times the amount of cisplatin that could be delivered by plain arterial infusion could be accumulated at the site of the tumor. Our previous study showed that the concentration of cisplatin in plasma that had perfused through the vesical region was 8-10 μg/ml after intra-arterial injection of 300 mg. This suggests that the vesical tumor was exposed to a cisplatin perfusate equivalent to an LD100 drug concentration, based on data reported from various studies including phase I clinical trials (31), animal studies (32) and our own laboratory studies, thus achieving a markedly pronounced cytocidal effect against malignant cells. Several studies have revealed that primary lymphatic drainage of bladder cancer extends into the pelvic lymph nodes including internal iliac, external iliac, obturator, and presacral LNs. Secondary drainage progresses into the common iliac LNs and then into the paraaortic, interaortocaval, and paracaval LNs (23,33,34). The anticancer agent delivered by BOAI may also drain into the pelvic lymph nodes, thus ensuring a high concentration of the agent perfusing the pelvic area.

In addition to direct induction of cancer cell death by a high concentration of cisplatin, enhanced radiosensitivity of the cancer cells due to BOAI-induced hypoxia may also contribute to the good response achieved with this treatment regimen. Cisplatin is a well known radiosensitizer, which facilitates cell death by inhibiting the repair of radiotherapy-induced DNA damage, and/or may damage genes known to be related to radiosensitivity, e.g., BRCA2, and hMLH1, thereby enhancing sensitivity to radiation therapy and eventually leading to apoptosis (35-38). As several basic research studies have demonstrated that hypoxia markedly enhances cisplatin-induced radiosensitivity (35,37), the BOAI system, which provides not only a high concentration of anticancer agent, but also causes severe hypoxia at the tumor site as well as the pelvic area, may also largely contribute to the very efficient antitumor effect.

Using a rat model established by us, we recently investigated the mechanisms responsible for the effect of BOAI with an anticancer agent and irradiation. Our results have indicated that the concentration of anticancer agent delivered by BOAI is >10-fold higher in the pelvic lymphatics than is the case for intravenous injection (data not shown).

The other advantage of the OMC regimen, especially for patients with locally advanced cancer, is that it can deliver a high dosage of anticancer agent to the target area without severe systemic side effects, in view of the use of hemodialysis (HD). HD removes any non-protein-bound Pt immediately after passage of cisplatin through the pelvic area, and is also efficient for elimination of gemcitabine, as both protein-unbound cisplatin and gemcitabine have a molecular weight of approximately 300, similar to that of creatinine. Moreover, the anatomic structure and blood supply of the bladder may largely account for the efficient drainage of an anticancer agent achieved with this approach. As the urinary bladder is situated at the base of the pelvis, the relatively close circuit formed by the internal iliac artery, bladder, and common iliac veins may contribute to efficient drainage of the anticancer agent, thus increasing its elimination efficiency without influencing the systemic circulation. Indeed, we have previously shown that >95% of free Pt was efficiently eliminated by HD (9), which may allow administration of 200 mg of cisplatin concomitant with 1000 mg of gemcitabine without any severe side effects.

Thus, the OMC regimen, which delivers an extremely high concentration of anticancer agent to the site of a tumor, as well as the pelvic area, without causing severe adverse

systemic effects, can be regarded as a new therapeutic option for patients with macroscopic lymph node involvement, especially those with N1 stage disease. This therapy would offer the chance of cure not only for patients scheduled for treatment such as surgery after neoadjuvant chemotherapy, but also those for whom total cystectomy is not indicated because of advanced disease, advanced age, poor performance status or other reasons, and are thus considered physically incapable of tolerating the chemotherapeutic regimens that are usually applied clinically. This therapy would improve the feasibility of radical cure even without the need for cystectomy in patients for whom such surgery would otherwise be necessary, and also facilitate potential cure in patients whose condition would normally rule out this likelihood and for whom, otherwise, merely palliative treatment would seem the only option.

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