A great option for elderly patients with locally invasive bladder cancer, BOAI-CDDP-radiation (OMC regimen)

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Abstract. We have developed a novel bladder preservation therapy, balloon-occluded arterial infusion (BOAI) of cisplatin/gemcitabine, concomitantly with hemodialysis, along with concurrent irradiation [the so-called 'OMC (Osaka Medical College) regimen']. The OMC regimen delivers an extremely high concentration of anticancer agent to the site of a tumor without systemic adverse effects, since more than 95% of free Pt was efficiently eliminated by hemodialysis, which enables short hospital stay. In this study, we investigated the efficiency of OMC regimen in patients aged over 70 years with muscle-invasive bladder cancer without metastasis. A total of 134 such patients were assigned to receive either the OMC regimen (n=89) or cystectomy (n=45). OMC regimen patients who failed to achieve CR underwent cystectomy, or secondary BOAI with gemcitabine (1,600 mg). The OMC regimen, which delivers an extremely high concentration of anticancer agent to the tumor site without systemic adverse effects, yielded CR in >91% (81/89) of patients. More than 96% (78/81) of the CR patients survived without recurrence with intact bladder after a mean follow-up of 164 (range 16-818) weeks. The 5- and 10-year bladder intact survival rates were 87.2 and 69.8%, and overall survival rates were 88.4 and 70.7% (vs. 59.9 and 33.3% for cystectomy, p=0.0002), respectively, although the median age in the OMC regimen group was significantly greater than in the cystectomy group (median, range = 77, 70-98 vs. 74, 70-89; p=0.0003). No patients suffered grade II or more severe toxicities; the oldest patient, aged 91 years, successfully completed this therapy. In conclusion, the OMC regimen is a useful bladder preservation strategy for elderly patients with locally invasive bladder cancer, not only in those for whom cystectomy is indicated, but also in patients whose condition is not amenable to curative treatment and for whom palliation would otherwise seem the only option.

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

Key words: balloon-occluded-arterial-infusion, hemodialysis, invasive bladder cancer, trimodality therapy, elderly patient

Introduction

The gold standard of therapy for locally invasive bladder cancer (T2-4, N0M0) is radical cystectomy. However, approximately 80% of cases of bladder cancer are diagnosed in individuals over the age of 60 (1). Many of these patients may be at risk of various conditions such as heart and lung disease (2), and are therefore deemed poor candidates for surgery because of their medical comorbidities.

Trimodality therapy involving radical transurethral resection, chemotherapy and radiation therapy has long been attempted as an alternative approach for patients who require cystectomy. The Radiation Therapy Oncology Group (RTOG) has completed six prospective protocols entering 415 patients with T2-T4a muscle-invasive bladder cancer who were candidates for cystectomy. However, none of the protocols achieved a 5-year survival rate of more than 60% (3-9). Moreover, the 5-year bladder intact survival rates were less than 50% in most of studies (8-11). Improvement of the survival rate with bladder preservation may require a new method, which allows to deliver a higher dosage of anticancer agent specifically into the tumor, without causing systemic side-effects.

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). 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. We have previously reported that all elderly patients (aged 98 years) completed this regimen, and that more than 90% of patients with locally advanced urothelial bladder cancer who were treated in this way achieved CR (12). The OMC regimen, which enables short hospital stay, can be regarded as a curative therapy for elderly patients, not only those for whom total cystectomy is indicated, but also those of whom total cystectomy is not feasible because of age, performance status or other reasons and who are considered physically incapable of tolerating the chemotherapeutic regimens that are usually applied clinically. Herein, we describe this novel approach and its outcomes to date for elderly patients (n=89) in comparison with total cystectomy (n=45).

Patients and methods

Eligibility criteria. Eligible patients were aged over 70 years and had histologically confirmed stage CIS, T2 or T3 muscle-invasive bladder cancer without 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. 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.

Study design and treatment. Before study entry, patients underwent transurethral resection of the bladder tumor (TURBT) to establish the diagnosis. We primarily recommended total cystectomy when surgery was feasible. However, the OMC regimen was offered as another treatment option whenever total cystectomy was not feasible because of advanced age, performance status or other reasons. Patients were assigned to receive the OMC regimen at 4 to 5 weeks after TURBT to allow adequate healing.

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 in the bladder was deemed as treatment failure, and such patients were primarily advised to undergo total cystectomy when possible, but otherwise to undergo secondary BOAI with a higher dosage of cisplatin or gemcitabine (1,600 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).

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 at 6-month intervals thereafter.

Statistics. Simple as well as multiple regression analyses were conducted to evaluate the significance of the following variables as risk factors of treatment failure: age, sex, patient performance status, tumor stage and tumor size, and significance of complete resection of tumor and hydronephrosis due to tumors are also evaluated. The life table probabilities of overall survival and progression-free survival were determined using Kaplan-Meier analysis and log-rank test. The Cox proportional hazards regression analysis 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 2013, 89 (63 males and 26 females) were treated with the OMC regimen, and 45 (39 males and 6 females) underwent radical cystectomy. The characteristics of the patients in these two treatment groups are shown in Table I. For preoperative clinical staging, we used a simplified form of the 2002 TNM classification to stage bladder tumors as Tis, T1, T2 and T3 (13). To make a valid comparison, preoperative clinical staging and not the pathologic stage after cystectomy was used to compare the two treatment groups, thus avoiding stage migration that may occur after pathologic staging (14).

Treatment details

OMC regimen group. Patients assigned to the OMC regimen group underwent transurethral resection of the bladder tumor (TURBT) to establish the diagnosis. They were then scheduled to receive the OMC regimen 4 to 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.

Table I. Patient characteristics of both groups.

Characteristics	OMC regimen	Total cystectomy	P-value
Age, median (range years)	77 (70-91)	74 (70-89)	0.0003
Sex			
Male (%)	63 (70.8%)	36 (86.7%)	0.0469
Female (%)	26 (29.2%)	9 (13.3%)	
ECOG performance status			
0	35 (39.4%)	13 (28.9%)	NS, 0.4063
1	39 (43.8%)	25 (55.6%)	
2	15 (16.8%)	7 (15.6%)	
Clinical stage			
T-stage			
Cis	5 (5.6%)	3 (6.6%)	NS, 0.7929
T2	47 (52.8%)	26 (57.8%)	
T3	37 (41.6%)	16 (35.6%)	

NS, not significant.

Table II. Criteria for the administration of cisplatin.

In the initially enrolled 11 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 151 patients	
100 mg	All patients

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. The extracorporeal circuit used in the treatment was illustrated in our previous paper (15). Various amounts of cisplatin (100, 200 or 300 mg) were locally infused through the catheter over a 1-h period (Table I). 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 x 25 days) followed by 10 Gy (2 Gy/day x 5 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.

Radical cystectomy group. Among the 45 patients in the radical cystectomy group, 27 patients underwent uretero-cutaneostomy, 12 underwent ileal conduit formation, 4 underwent continent urinary diversion with ileal-neobladder formation (Hartmann's method), 1 underwent Indiana pouch formation, and the remaining 1 underwent uretero-sigmoidostomy performed at the time of radical cystectomy. Standard pelvic lymphadenectomy was performed in 39 patients, five patients underwent iliac sampling, and one patient was not studied in sufficient detail to allow assessment of the level of lymph node dissection. As not all of the histology reports mentioned the number of lymph nodes examined, it was not possible to precisely evaluate the extent of dissection. There were no significant differences in cause-specific or overall survival between the patients who underwent nodal dissection and the patients who did not. Urethrectomy was performed in 9 patients at the time of radical cystectomy because of the presence of extensive carcinoma *in situ* or multifocal bladder tumors.

Response to the OMC regimen. Table III summarizes the treatment response, duration of response, and patient characteristics, including sex, age, tumor stage, tumor size, involvement of hydronephrosis, performance status and success or failure of complete TURBT. Overall, 81 of the 89 patients (91.0%, 95% CI, 83.1-91.0%) achieved a complete response as defined by the absence of persistent disease revealed by cystoscopy, biopsy, and urine cytology after therapy (Table III). More than 96% 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 166 weeks (range, 16-818 weeks; 1st to 3rd Qu = 69-245 weeks) from the completion of therapy.

The univariate as well as multivariate regression analyses revealed that a hydronephrosis and tumor histology (UC) are the only risk factor for treatment failure, while tumor stage, tumor size, and failure of complete resection of tumor, those usually have been reported as risk factors for treatment failure of bladder preservation therapy, were not selected (Table IV).

Comparison of survival between the two groups

Overall survival. Overall survival was significantly improved in the OMC regimen group, with 5- and 10-year survival rates of 88.4 and 70.7%, respectively as compared to 59.9 and 33.3% in the cystectomy group, p=0.0002, Fig. 1A). Fig. 1B, C and D show OS ratio of patients in each T-stage of CIS, T2 and T3, respectively. The OS ratio in patients with T2 as well as T3

Table III. Response at 3 months after treatment and current outcome.

	CR			PR			SD			PD		
	No	%	95%-CI	No	%	95%-CI	No	%	95%-CI	No	%	95%-CI
Total number of patients	81	91.0	83.1-96.0	4	4.49	1.24-11.1	2	2.25	0.27-7.88	2	2.25	0.27-7.88
Duration of response												
Mean, range	164, 16-818 weeks			124, 36-231 weeks			56, 18-94 weeks			0 weeks		
1st, 3rd Qu	67, 237 weeks			83, 156 weeks			37, 75 weeks			0 weeks		
Recurrence	3	3.70	0.77-10.4	0	0	0-60.2	2	100	15.8-100			
Death	4	4.94	1.36-12.2	1	25.0	0.63-80.6	2	100	15.8-100	2	100	15.8-100
Age (mean, range)	77, 70-91 years			77, 73-78 years			79, 76-81 years			78, 77-79 years		
Sex												
Male	58	71.6	60.5-81.1	3	75.0	19.4-99.4	1	50.0	12.6-98.7	1	50.0	12.6-98.7
Female	23	28.4	18.9-39.5	1	25.0	0.63-80.6	1	50.0	12.6-98.7	1	50.0	12.6-98.7
Categories												
T-stage												
Tis	5	6.17	2.03-13.8	0	0	0-60.2	0	0	0-84.2	0	0	0-84.2
2	46	56.8	45.3-67.8	1	25.0	0.63-80.6	0	0	0-84.2	0	0	0-84.2
3	30	37.0	26.6-48.5	3	75.0	19.4-99.4	2	100	15.8-100	2	100	15.8-100
Tumor size												
≤3 cm	41	50.6	39.3-61.9	2	50.0	6.76-93.2	0	0	0-84.2	1	50.0	12.6-98.7
3-5 cm	38	46.9	35.7-58.3	1	25.0	0.63-80.6	2	100	15.8-100	1	50.0	12.6-98.7
>5 cm	2	2.47	0.30-8.64	1	25.0	0.63-80.6	0	0	0-84.2	0	0	0-84.2
Hydro												
(+)	3	3.70	0.77-10.4	2	50.0	6.76-93.2	1	50.0	12.6-98.7	0	0	0-84.2
(-)	78	96.3	89.6-99.2	2	50.0	6.76-93.2	1	50.0	12.6-98.7	0	0	0-84.2
Comp-TUR												
(+)	58	71.6	60.5-81.1	2	50.0	6.76-93.2	1	50.0	12.6-98.7	1	50.0	12.6-98.7
(-)	23	28.4	18.9-39.5	2	50.0	6.76-93.2	1	50.0	12.60-98.7	1	50.0	12.6-98.7
PS												
0	33	40.7	29.9-52.2	1	25.0	0.63-80.6	0	0	0-84.2	1	50.0	12.6-98.7
1	33	40.7	29.9-52.2	3	75.0	19.4-99.4	2	100	15.8-100	1	50.0	12.6-98.7
2	15	18.5	10.8-28.7	0	0	0-60.2	0	0	0-84.2	0	0	0-84.2

Hydro, hydronephrosis; comp-TUR, complete TURBT.

tumors was significantly better in the OMC regimen group, although statistically significance has not seen in patients in with CIS (despite of 100% of OS), because of short follow-up period.

Progresion-free survival. The progression-free survival ratio was also significantly better in the OMC regimen group in total patients, as well as in each patients with CIS, T2 and T3 tumors (Fig. 2). In all patients, more than 87.2 and 69.8% of patients have been surviving with their functioning bladder at 5- and 10-years, respectively; this is the most important issue for the bladder preservation therapy.

Predictors of patient survival selected using univariate and multivariate Cox regression analyses in OMC regimen group. We investigated the significance of each factor, including sex, age, tumor stage, tumor size, tumor pathology (non-UC vs. UC), involvement of hydronephrosis, performance status (2 vs. 0-1), and success or failure of complete TURBT as a predictor of overall survival and progression-free survival using the Cox regression model. As shown in Table V, univariate Cox regression analysis selected hydronephrosis, tumor histology and greater than 5 cm of tumor size as the significant factors affecting both overall and progression-free survival, while tumor stage and failure of complete resection of tumor have not been selected. Multivariate Cox regression analysis also selected hydronephrosis and tumor histology as the significant factors affecting both overall and progression-free survival, while tumor size, tumor stage and failure of complete resection of tumor have not been selected.

Toxicity. The most significant outcome of the OMC regimen was that its related toxicity was markedly less severe than

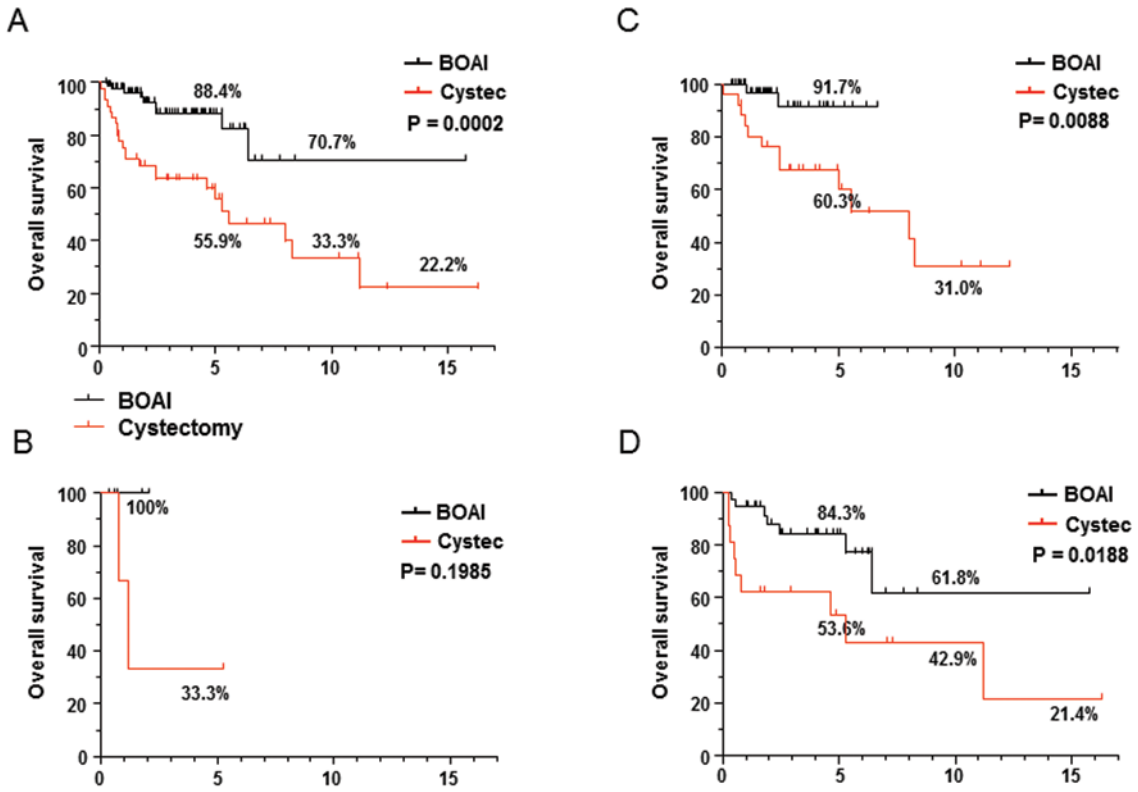

Figure 1. Comparison of overall survival between the OMC regimen and cystectomy groups. Kaplan-Meier curves for overall survival in (A) all patients, patients with tumor of (B) CIS, (C) T2 and (D) T3 are shown, respectively.

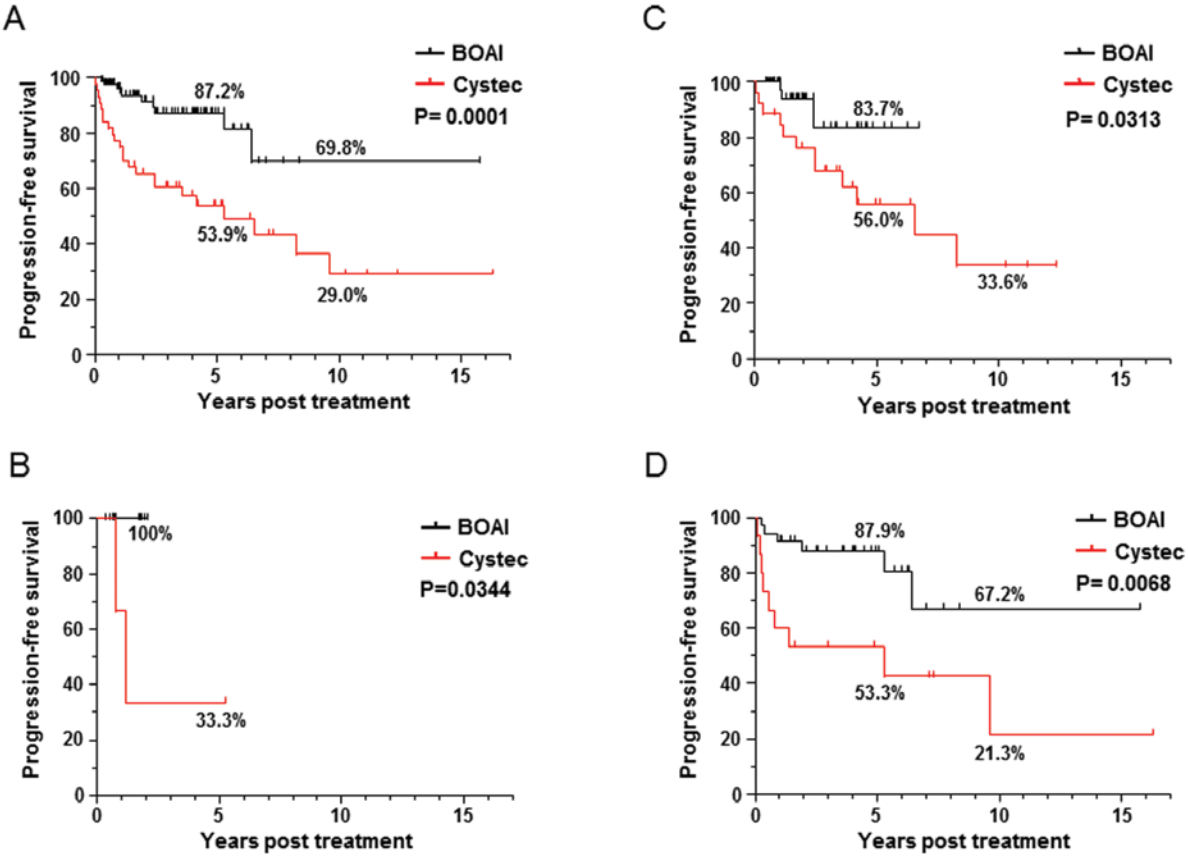

Figure 2. Comparison of progression-free survival between the OMC regimen and cystectomy groups. Kaplan-Meier curves for overall survival in (A) all patients, patients with tumor of (B) CIS, (C) T2 and (D) T3 are shown, respectively.

Table IV. Risk factors for treatment failure in the OMC regimen group.

		Univariate		Multivariate	
	Category	Odds ratio	P-value	Odds ratio	P-value
Hydronephrosis	(+) vs. (-)	15.63	0.0034	200	0.0045
T-stage (T3)	T3 vs. <T3	11.90	0.0235	14.71	0.0488
Tumor histology	UC vs. non-UC	13.17	0.0176	56.38	0.0426
Tumor size	≥3 cm vs. <3 cm	1.708	0.4830	10.42	0.2238
Tumor size	≥5 cm vs. <5 cm	5.650	0.1787	NV	NV
Tumor number	Cont. variable	2.002	0.1307	4.533	0.0912
Complete TUR	Yes vs. no	1.513	0.5911	2.290	0.6316
Performance status	2 vs. 0-1	485,376	0.9798	290,745	0.9985
Sex	Male vs. female	2.500	0.1749	2.985	0.2628
Age	Cont. variable	1.513	0.5911	1.111	0.4653

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

Table V. Predictors of overall survival and progression-free survival in the OMC regimen group evaluated by univariate and multivariate Cox regression analyses.

A, Overall survival.

		Univariate		Multivariate	
	Category	Odds ratio	P-value	Odds ratio	P-value
Hydronephrosis	(+) vs. (-)	9.524	0.0081	23.81	0.0068
Histology	UC vs. non-UC	7.649	0.0031	44.08	0.0093
T-stage	T3 vs. <T3	1.887	0.3154	2.469	0.3339
Tumor size	≥3 cm vs. <3 cm	1.500	0.5727	1.428	0.7964
Tumor size	≥5 cm vs. <5 cm	11.63	0.0035	5.974	0.1253
Tumor number	Cont. variable	1.387	0.4103	1.880	0.3157
Complete TUR	Yes vs. no	1.005	0.9938	1.051	0.9741
Performance status	2 vs. 0-1	1.376	0.6925	2.766	0.3883
Sex	Male vs. female	2.372	0.1392	1.539	0.5813
Age	Cont. variable	1.061	0.4597	1.259	0.0644

B, Progression-free survival.

		Univariate		Multivariate	
	Category	Odds ratio	P-value	Odds ratio	P-value
Hydronephrosis	(+) vs. (-)	9.173	0.0016	10.99	0.0195
Histology	UC vs. non-UC	7.649	0.0031	12.492	0.0112
T-stage	T3 vs. <T3	1.887	0.3154	1.323	0.6849
Tumor size	≥3 cm vs. <3 cm	1.583	0.4590	2.659	0.2486
Tumor size	≥5 cm vs. <5 cm	62.29	0.0158	6.098	0.1809
Tumor number	Cont. variable	1.115	0.7458	1.063	0.9011
Complete TUR	Yes vs. no	1.456	0.5601	5.291	0.0989
Performance status	2 vs. 0-1	1.543	0.5167	1.443	0.6853
Sex	Male vs. female	2.372	0.1392	1.143	0.8582
Age	Cont. variable	1.022	0.7476	1.128	0.1426

Cont. variable, continuous variable.

Table VI. Toxicity.

	Grades			Duration (days)		
Toxicity	1 No. (%)	2 No. (%)	3-4 No. (%)	<3 No. (%)	3-7 No. (%)	>7 No. (%)
Blood/bone marrow						
Total	6 (6.7)	2 (2.2)	0			
Granurocytepenia	5 (5.6)	0	0	0	4 (4.5)	1 (1.1)
Anemia	6 (6.7)	2 (2.2)	0	3 (3.4)	4 (4.5)	1 (1.1)
Gastrointestinal						
Total	15 (16.9)	0	0			
Anorexia	10 (11.2)	0	0	6 (6.7)	4 (4.5)	0
Constipation	6 (6.7)	0	0	5 (5.6)	1 (1.1)	0
Diarrhea	5 (5.6)	0	0	2 (2.2)	3 (3.4)	0
Nausea	11 (12.4)	0	0	6 (6.7)	5 (5.6)	0
Vomiting	1 (1.1)	0	0	0	1 (1.1)	0
Neuropathy	2 (2.2)	1 (1.1)	00	0	0	3 (3.4)

those reported for other protocols, as shown in Table VI. None of the patients suffered grade III or more severe toxicity. Eight patients (8.99%, 95% confidence interval (CI), 3.96-16.9%) experienced grade I blood/bone-marrow toxicity, 15 (16.9%, 95%CI, 9.75-26.3%) had gastrointestinal toxicity, and 3 (2.25%, 95%CI, 0.27-7.88%) had neuropathy. The duration of blood/bone-marrow toxicity, including granulocytopenia and anemia, was relatively short: median duration was 5 days for granulocytopenia (range 3-9 days) and 4 days for anemia (range 2-10 days). No patient received granulocyte colony-stimulating factor or transfusion of red blood cells. Gastrointestinal toxicity included anorexia in 10 patients, constipation in 6, diarrhea in 5, nausea in 11, and vomiting in 1, but all symptoms disappeared within 6 days after intra-arterial infusion. One patient experienced grade II neuropathy in the peroneal nerve area, but this disappeared by the 12 months after the treatment. There were no other adverse reactions such as renal failure, genitourinary toxicity, radiation cystitis or life-threatening complications.

Discussion

Optimal initial treatment for muscle-invasive bladder cancer in elderly patients has been a subject of debate. Some urologists or radiologists have recommended bladder-sparing trimodality approaches with aggressive transurethral resection of the bladder tumor (TURBT) and radiochemotherapy, while others have advocated immediate cystectomy (3-7). Nielsen *et al* reviewed the records of 888 patients with transitional cell carcinoma who underwent radical cystectomy and pelvic lymphadenectomy for localized disease at three institutions (16), and found that advanced age was independently and significantly associated with more pathologically advanced disease and poorer bladder-specific mortality after surgery. The actuarial 5-year overall survival rate of such patients over 70 years of age has reportedly ranged from 35 to 60% (3-9). A highly effective, but non- or minimally invasive therapy that conserves the bladder is therefore needed.

BOAI allows delivery of an extremely high concentration of anticancer agent to the bladder and surrounding pelvic region (17-19). In addition, severe hypoxia in the target region resulting from BOAI may play a role in the marked antitumor effect, as several basic studies have demonstrated that hypoxia greatly enhances the effectiveness of cisplatin (20,21). Enhanced radiosensitivity of the cancer cells due to the BOAI-induced high concentration of cisplatin may also contribute significantly to the good response achieved. Such theories may be supported by the present outcomes; more than 90% of patients achieved CR, and most of the CR patients (96%) survived with their intact bladder; the 5- and 10-year bladder intact survival rates were 87.2 and 69.8%, respectively. Additionally, the findings from our *in vivo* experiments, demonstrating that BOAI provided an extremely high concentration of anticancer agent to the bladder and surrounding pelvic region, as well as to the para-aortic lymphatic tissues (data not shown) may also contribute to the excellent outcomes even better than cystectomy.

The other advantage of the OMC regimen, especially pertinent for the elderly patients, is a significant reduction of systemic side-effects. Cisplatin exerts its antitumor activity via the non-protein-bound form, which reduces steeply after administration: its half-life is normally less than 60 min, and reaches to below the detection limit 4 h after administration (22,23). The most important point of OMC regimen is a removal of non-protein-bound Pt immediately after administration of cisplatin by performing HD via the common iliac veins, which accomplish efficient drainage of cisplatin immediately after passage through the tumor. HD is specifically efficient for cisplatin elimination, since the molecular weight of protein-unbound cisplatin is 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 cisplatin 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 the elimination efficiency without influencing the systemic circulation. Indeed, we have previously found that >95% of free Pt was efficiently eliminated by HD, which may allow the present outcomes that all elderly patients, even over 90 years old patients, completed this regimen. Thus, it is noteworthy that this therapy will improve the feasibility of radical cure 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.

In conclusions, the OMC regimen, which delivers an extremely high concentration of anticancer agent to the site of a tumor without causing systemic adverse effects, can be regarded as a curative therapy for elderly patients, not only those for whom total cystectomy is indicated, but also those of whom total cystectomy is not feasible because of age, performance status or other reasons and who are considered physically incapable of tolerating the chemotherapeutic regimens that are usually applied clinically.

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