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Review Article

Neoadjuvant and adjuvant chemotherapy for locally advanced bladder carcinoma: Development of novel bladder preservation approach, Osaka Medical College regimen

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Abbreviations & Acronyms
ABC = advanced bladder cancer
BOAI = balloon-occluded arterial infusion
CDDP = cisplatin
CMV = cisplatin, methotrexate, vinblastine
CR = complete response
GC = gemcitabine and cisplatin
HD = hemodialysis
MRI = magnetic resonance imagery
M-VAC = methotrexate, vinblastine, adriamycin-doxorubicin and cis-platinum
NC = no change
OS = overall survival
PCr = phocreatine
TUR-BT = transurethral resection of the bladder tumor
UC = urothelial carcinoma

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Abstract: Cisplatin-based chemotherapy has been widely used in a neoadjuvant as well as adjuvant setting. Furthermore, trimodal approaches including complete transurethral resection of the bladder tumor followed by combined chemotherapy and radiation have generally been performed as bladder preservation therapy. However, none of the protocols have achieved a 5-year survival rate of more than 70%. Additionally, the toxicity of chemotherapy and/or a decreased quality of life due to urinary diversion cannot be ignored, as most patients with bladder cancer are elderly. We therefore newly developed the novel trimodal approach of "combined therapy using balloon-occluded arterial infusion of anticancer agent and hemodialysis with concurrent radiation, which delivers an extremely high concentration of anticancer agent to the site of a tumor without systemic adverse effects ("Osaka Medical College regimen" referred to as the OMC regimen). We initially applied the OMC regimen as neoadjuvant chemotherapy for locally advanced bladder cancer. However, since more than 85% of patients with histologically-proven urothelial cancer achieved complete response with no evidence of recurrence after a mean follow-up of 170 (range 21–814) weeks, we have been applying the OMC-regimen as a new approach for bladder sparing therapy. We summarize the advantage and/or disadvantage of chemotherapy in neoadjuvant as well as adjuvant settings, and show the details of our newly developed bladder sparing approach OMC regimen in this review.

Key words: balloon-occluded arterial infusion, hemodialysis, invasive bladder cancer, OMC regimen.

Introduction

The biological behavior of muscle-invasive bladder cancer differs from that of non-muscle invasive bladder cancer, with life-threatening metastases developing in more than 50% of patients.[1–3] Despite radical cystectomy with pelvic lymph node dissection, which represents the gold standard for treating muscle-invasive bladder cancer, the 5-year survival rates of patients with pT2, pT3a, pT3b, and pT4 bladder cancer are 63–83%, 50–69%, 15–29%, and 21–22%, respectively.[1–3] About 50% of all patients with T2-T4 invasive bladder cancer die.

Cisplatin-based chemotherapy has been widely used in a neoadjuvant as well as adjuvant setting, since bladder cancer is considered to be a chemosensitive malignancy, and chemotherapy offers an overall survival (OS) benefit. Furthermore, trimodal approaches, including complete TUR-BT followed by combined chemotherapy and radiation, have generally been performed as bladder preservation therapy. However, none of the protocols employed have achieved a 5-year survival rate of more than 70%. Additionally, the toxicity of chemotherapy or a decreased quality of life, or both, due to urinary diversion, cannot be ignored, as most patients with bladder cancer are elderly.

We have developed a novel trimodal approach involving combined therapy using balloon-occluded arterial infusion (BOAI) of an anticancer agent and hemodialysis with concurrent

irradiation, which delivers an extremely high concentration of the anticancer agent to the site of a tumor without systemic adverse effects (the Osaka Medical College regimen, referred to here as the "OMC regimen"). We initially applied the OMC regimen as neoadjuvant chemotherapy for locally advanced bladder cancer. However, since more than 85% of patients with histologically proven urothelial cancer achieved a complete response (CR) with no evidence of recurrence after a mean follow up of 170 (range 21–814) weeks, we have been applying the OMC regimen as a new form of bladder-sparing therapy. In this review, we describe the details and effects of this newly developed bladder-sparing approach.[4–7]

Chemotherapy

The survival advantage of the methotrexate, vinblastine, adriamycin-doxorubicin and cis-platinum (M-VAC) chemotherapy has been supported by two randomized controlled trials with level one evidence.[8,9] However, the combination of gemcitabine and cisplatin (GC) has become a standard chemotherapy,[8,10–13] due to the significant toxicity associated with M-VAC therapy, including febrile neutropenia, mucositis and a toxicity death rate of 3–4%. A randomized study of M-VAC in comparison with GC demonstrated a similar response rate (GC 49% and M-VAC 46%; $P = 0.51$), progression-free survival (GC, 7.7 months and M-VAC, 8.3 months; $P = 0.63$), and median survival (GC, 14 months and M-VAC, 15.2 months; $P = 0.66$), with a better safety profile and tolerability for the GC regimen. Chemotherapy options in a neoadjuvant or adjuvant setting for invasive bladder cancer are described below.

Neoadjuvant chemotherapy

Chemotherapy in a neoadjuvant setting offers several advantages. Tolerability is better before than after surgery. Neoadjuvant chemotherapy also allows the primary tumor to be evaluated *in vivo* for response and assessment of whether it is sensitive to the regimen that is being administered.[14] Moreover, it allows for tumor downstaging, which may make surgery technically easier and increase the likelihood of resectability.[15]

A series of prospective, randomized phase III studies have evaluated the role of neoadjuvant chemotherapy plus definitive local therapy *vs* definitive local therapy alone.[16–19] In many cases, the local therapy was radical cystectomy. One of the most representative studies was the Southwest Oncology Group (SWOG) 8710 trial, details of which were reported by Grossman *et al*. in the *New England Journal of Medicine* in 2003.[16] That study demonstrated prolonged median survival (77 *vs* 46 months) and improved OS (57 *vs* 43%) at 5 years ($P = 0.06$) in patients who received three cycles of M-VAC in a neoadjuvant setting, in comparison with radical cystectomy alone. Comparable results were also obtained with cisplatin, methotrexate, vinblastine (CMV) regimens in the European Organisation for Research and Treatment of Cancer/Medical Research Council (EORTC/MRC) study, with a 5.5% survival benefit.[17] Furthermore, three separate meta-analyses have confirmed the benefit of stable disease in patients with bladder cancer. The first advanced bladder cancer (ABC) meta-analysis demonstrated a 5% absolute survival benefit (50 *vs* 45%) at 5 years ($P = 0.016$) for platinum-based combination therapy.[20] The second meta-analysis of platinum-based combination therapy revealed a 5% improvement in OS ($P = 0.003$), a 14% decrease in the risk of death from disease, and a 9% improvement in disease-specific survival ($P = 0.0001$) at 5 years in the updated ABC article published in 2005.[21] Finally, a Canadian meta-analysis also reported a 6.5% absolute improvement in survival ($P = 0.006$) with platinum-based combination therapy.[22]

When M-VAC and GC were compared head-to-head in a non-inferiority trial, von der Maase *et al*. obtained a similar median OS (14 *vs* 15.2 months; $P = 0.66$), a 5-year OS (13 *vs* 15.3%; $P = 0.53$) and a 5-year progression-free survival (9.8 *vs* 11.3%; $P = 0.63$)[10,11] in patients with metastatic bladder cancer. Since GC was shown to be associated with significantly less toxicity, there has been an active push towards substituting M-VAC with GC, even in no change (NC). This extrapolation may be potentially flawed, especially when considering how these two groups differ in terms of performance status and disease biology, as well as the primary goal, which is a cure in patients who receive NC treatment, rather than palliation and prolongation of survival when chemotherapy is administered in the presence of metastases. As such, Weight *et al*. chose to direct their attention towards evaluating NC (primarily with GC) using phosphocreatine (PCr) as an end point and surrogate parameter for survival.[23] In fact, the utility of CR as a surrogate for survival has been proven in several studies, including the SWOG 8710 study where patients that were downstaged to pT_0 (CR) following NC achieved an improved 5-year OS (85%); 38% of patients who received M-VAC chemotherapy had no evidence of cancer or PCr, compared with only 15% of those who underwent a radical cystectomy alone, who achieved pT_0 ($P < 0.001$).[16] A similar PCr rate was achieved in the EORTC/MRC study following CMV NC (32%).[17] However, in that study from the Cleveland Clinic, the authors reported a PCr of 7% with GC, which was well below the rates achieved in previous platinum-based combination NC studies.

Adjuvant chemotherapy

Conversely, there are also some disadvantages in the neoadjuvant setting. First, the evaluation of response is difficult since there is a large discrepancy (up to 30%) between

clinical and pathological staging.[24] Second, patients may be subjected to overtreatment, as 40–50% will have pathological organ confined disease and will not need such therapy. Third, although there is level one evidence in support of neoadjuvant chemotherapy, as discussed previously, the magnitude of the benefit seen in those studies was fairly small; in the order of 5%. To achieve a 5% advantage it is necessary to treat a large number of patients who may not have a high risk of recurrence, such as those with organ confined, node-negative disease for whom the recurrence-free rates are in the order of 70% or higher in large, long-term series. Fourth, administration of neoadjuvant chemotherapy may delay surgical intervention after diagnosis, thus leading to worse outcomes.[25] Several reports have now indicated that a delay of over 3 months from the time of diagnosis to radical cystectomy is associated with a worse outcome, and it is argued that in patients who are not responding to chemotherapy, this can in effect translate into a 3-month or more delay in proceeding to surgery.[26–29] Fifth, it may potentially be associated with higher perioperative morbidity and mortality.[30]

A number of prospective, randomized phase III clinical trials have demonstrated a statistically significant survival benefit of adjuvant chemotherapy for high-risk patients after radical cystectomy.[29,31,32] Skinner *et al*. randomized 91 patients after radical cystectomy to observation versus chemotherapy utilizing cisplatin, doxorubicin and cyclophosphamide, and demonstrated the benefit of adjuvant chemotherapy, with a 3-year disease-free survival of 70 versus 46%, as well as a median survival of 4.3 versus 2.4 years ($P = 0.006$).[29] Stockle *et al*. randomized 49 patients after surgery to either multi-agent chemotherapy (M-VAC or methotrexate, vinblastine, epirubicin and cisplatin (M-VEC)) or observation, and published several reports after progressively longer follow-up periods, demonstrating the advantage of adjuvant chemotherapy; most recently reported by Lehmann *et al*. with a 10-year OS and disease-free survival of 41.7% in the chemotherapy arm versus 17.4% in the observation arm, despite some weaknesses of the study in terms of its small numbers and the fact that more than half of the patients had pN(+) and T4 disease.[31,33–36] Moreover, Freiha *et al*. randomized 50 high-risk post-cystectomy patients with pathological T3 or T4 disease to observation or chemotherapy with the CMV regimen,[32] and found a significant improvement in median time-to-progression of 37 months for the chemotherapy group versus 12 months for the observation group despite there being no significant difference in OS (54 *vs* 34% at a median follow up of 62 months) due to the small number of patients and the fact that the study was closed early.

As mentioned above, data from some clinical trials support the use of adjuvant chemotherapy after cystectomy. However, all those trials have been hampered by the small numbers of patients enrolled in the study and problems with design. A recent meta-analysis by the Advanced Bladder Cancer Meta-Analysis Collaboration focused on data from 491 individual patients, in order to address the issue of small numbers.[37] This demonstrated an absolute 9% improvement in OS at 3 years in favor of adjuvant chemotherapy, and a 25% reduction in the risk of death based on a hazard ratio of 0.75 (95% CI: 0.60–0.96; $P = 0.019$). However, the number of patients included in the analysis, only 491, was relatively small in comparison to those in the neoadjuvant setting, which included almost 3000 patients. The meta-analysis for adjuvant chemotherapy showed a wide 95% CI of 0.60–0.96 (compared with 11–12% for neoadjuvant chemotherapy). It is hoped that a large-scale phase III randomized trial of adjuvant chemotherapy will be published soon.

Chemoradiotherapy

Systemic chemotherapy + radiotherapy

A combined treatment involving radical transurethral resection, chemotherapy and radiation therapy has been attempted as an alternative approach for patients who require cystectomy. Many clinical studies have been performed, including large-scale studies performed by the Radiation Therapy Oncology Group (RTOG) in the USA (six prospective studies were performed after 1985, involving 415 patients with T2-T4a invasive bladder cancer indicated for cystectomy).[38–43] The results of the main clinical studies are shown in Table 1.[38–52] The response rate varied slightly among the studies, but a CR was achieved in more than 60% of patients who were able to complete the therapy. Many studies have reported the stage (T-stage, T3 *vs* T2), histological type (non-urothelial carcinoma [UC] *vs* UC), grade (G3 *vs* G2), tumor size (3 cm or 5 cm or larger), number of tumors (multiple *vs* solitary), and presence or absence of carcinoma *in situ* and hydronephrosis as risk factors for treatment failure, and the importance of as deep an excision as possible in radical TUR-BT.[48,53–57] Regarding the irradiation dose, it has been suggested that a higher therapeutic effect can be obtained by adding local irradiation at a total dose of 60 Gy or higher, although no prospective study has obtained evidence for this. With regard to chemotherapy regimens, marked therapeutic effects of combination chemotherapy, such as the simultaneous administration of cisplatin (CDDP) and fluorouracil (5-FU) with irradiation,[49–51,58] and the addition of methotrexate + vinblastine + cisplatin (MCV) before and after surgery as adjuvant therapy for radiochemotherapy (RCT) (radiation therapy (RT) + CDDP), in comparison with cisplatin alone, have been suggested.[39,40,42] Weiss *et al*.[59] and Rodel *et al*.[49] reported a CR induction rate higher than 80%, but no significant difference was noted in the 5-year survival rate, and severe adverse effects of MCV adjuvant therapy markedly reduced the patients' quality of life, showing no usefulness in actual clinical cases. In RTOG 99–06 per-

Table 1 Systemic chemotherapy plus radiotherapy

References	Number of Pt	Chemotherapy	Radiation (Gy)	CR (%)	Overall survival (%, years)
RTOG 85–12 Tester (1993)[38]	42	CDDP	40–65	66	52 (5)
RTOG 88–02 Tester (1996)[39]	91	CDDP MCV (neoadj)	40–65	75	51 (5)
RTOG 89–03 Shipley (1998)[40]	123	CDDP ±MCV (neoadj)	40–65	59	49 (5)
RTOG 95–06 Kaufman (2000)[41]	34	CDDP 5FU (neoadj)	40–65	67	83 (3)
RTOG 97–06 Hagan (2003)[42]	52	CDDP MCV (neoadj)	64.8	74	61 (3)
RTOG 99–06 Kaufman (2009)[43]	84	CDDP PTX (neoadj) CDDP+GEM (adj)	64.3	81	56 (5)
TROG 97–01, 99–01 Gogna (2006)[44]	113	CDDP	63–64	70	50 (5)
Shipley (1987)[45]	70	CDDP	65	77	35 (4)
Prout (1990)[46]	53	CDDP	65	70	65 (3)
Sauer (1990)[47]	67	CDDP	50	76	66 (3)
Zietman (2001)[48]	190	CDDP	40	64	68 (5)
Rodel (2002)[49]	92	Carboplatin		66	45 (5)
	145	CDDP	45–69.4	82	62 (5)
	49	CDDP/5-FU		87	65 (5)
Chen (2003)[50]	23	CDDP+5-FU	55	74	69 (3)
Peyromaure (2004)[51]	43	CDDP+5-FU	68	77	63 (5)
Weiss (2007)[52]	112	CDDP+5-FU	40–65	88.4	74 (5)

5-FU, 5-fluorouracil; adj, adjuvant; CDDP, cisplatin; CR, complete response; GEM, gemcitabine; MCV, methotrexate + cisplatin + vinblastine; neoadj, neoadjuvant; PTX, paclitaxel; RTOG, Radiation Therapy Oncology Group; TROG, Trans-Tasman Radiation Oncology Group.

formed by Kaufman *et al*., the therapeutic effects of a multi-drug combination therapy were investigated. In addition to RCT with RT + CDDP, taxanes were administered as adjuvant therapy before RCT and a novel anticancer drug, gemcitabine, and CDDP were added concomitantly with adjuvant therapy after RCT (taxanes and gemcitabine have been suggested to show fewer adverse effects, while exerting strong anticancer effects), and CR was obtained at a rate of 81%, but the 5-year survival rate was only 56%, showing no apparent superiority of this regimen in long-term outcomes.[43]

Intra-arterial infusion of anticancer agent + radiotherapy

Eapen *et al*. initially reported that a combination of cisplatin intra-arterial infusion and radiotherapy achieved CR in more than 90% of patients.[60] Intra-arterial infusion was initially performed by Klopp *et al*. in 1950, aiming at elevating the tissue anticancer drug level,[61] and many clinical studies were performed thereafter, but no consistent consensus has been reached regarding differences in the anticancer effect between intra-arterial and i.v. infusions. However, Chen *et al*. compared the anticancer drug levels achieved by intra-arterial and i.v. infusions employing a physiological pharmacokinetic model: intra-arterial infusion significantly increased the local drug level, while reducing the systemic drug level.[62] Terashima *et al*. measured the level of cisplatin in the bladder mucosa when they performed TUR after the intra-arterial or i.v. infusion of cisplatin.[63] They found that the cisplatin level in the bladder mucosa was 2.7 times higher after intra-arterial infusion than that after i.v. infusion. Higa *et al*. also reported that when cisplatin was administered to dogs by intra-arterial infusion, the cisplatin levels in the bladder mucosa and external iliac lymph nodes were 2.5 and twice higher than when administered by i.v. infusion, respectively.[64] In fact, in clinical cases, several groups have reported that a combination of cisplatin-based intra-arterial infusion and radiotherapy achieved a CR in 70–90% of patients, and a 5-year survival rate higher than 70% in patients with invasive bladder cancer, as shown in

Table 2 Intra-arterial infusion of anticancer agent plus radiotherapy

References	Number of Pt	Chemotherapy	Radiation (Gy)	Complete response (%)	Overall survival (%, years)
Eapen (1989)[60]	25	CDDP	60 Gy	96	65 (2)
Eapen (1995)[65]	104	CDDP	60 Gy	90	65 (5)
Mokarim (1997)[66]	35	CDDP + ADM	60 Gy	74	77 (5)
Aota (1999)[67]	51	CDDP + ADM	20 Gy	84	(–)
Eapen (2004)[68]	200	CDDP	60 Gy	90	65 (5)
Sumiyoshi (2004)[69]	68	CDDP + THP	36 Gy	91	74 (5)
Miyanaga (2007)[70]	56	CDDP + MTX	Proton beam X-ray	81.4	70 (5)

ADM, doxorubicin; CDDP, cisplatin; MTX, methotrexate; THP, pirarubicin.

Table 2.[60,65–70] Although no apparent usefulness of intra-arterial infusion alone was observed in terms of the clinical outcome of the anticancer effect, it was assumed that intra-arterial infusion increased the tissue drug level, and that combination with irradiation potentiated the cytocidal effect, thus improving the clinical therapeutic effect. Large-scale prospective studies on the clinical therapeutic effects of intra-arterial infusion and radiotherapy are expected.

Novel bladder preservation therapy: the OMC regimen

Background

We have developed a novel trimodal approach involving a combination BOAI of an anticancer agent and HD with concurrent radiation, which delivers an extremely high concentration of anticancer agent to the site of a tumor without adverse systemic effects (the OMC regimen). We initially applied this regimen as neoadjuvant chemotherapy for locally advanced bladder cancer. However, since more than 85% of patients with histologically proven urothelial cancer achieved a CR with no evidence of recurrence after a mean follow-up of more than 3 years, we have been applying the OMC regimen as a new approach for bladder-sparing therapy.[4–7]

Treatment details

Patients underwent complete TUR-BT to establish the diagnosis, and were then scheduled to receive the OMC regimen 4 to 5 weeks after TUR-BT to allow adequate healing. We administered 100, 200, or 300 mg of cisplatin as a single bolus according to the criteria described in Table 3. 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 using the femoral arterial approach. 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, 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 the active flow of injected contrast medium into the urinary bladder. Figure 1 illustrates the extracorporeal circuit used in the treatment, and Figure 2 presents digital subtraction angiography images of the bilateral common iliac arteries before (a) and after (b) balloon occlusion. HD was performed simultaneously, 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 HD fluid flow rate was 500 mL/min.

Table 3 Criteria for the administration of cisplatin

In the 22 patients initially enrolled	
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 74 patients	
100 mg	all patients

SCr, serum creatinine.

Radiation therapy was administered to the whole pelvis using a computed tomography (CT)-planned three-

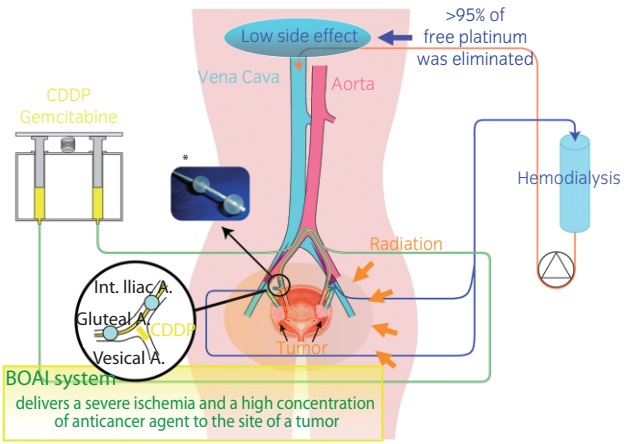

Fig. 1 Schema of the Osaka Medical College regimen. The extracorporeal circuit allowed balloon-occluded intra-arterial infusion of cisplatin/gemcitabine concurrent with hemodialysis. BOAI, balloon-occluded arterial infusion; CDDP, cisplatin.

dimensional conformal technique to a total of 60.4 Gy: 50.4 Gy (1.8 Gy/day × 28 days) followed by 10 Gy (2 Gy/day × 5 days) of local irradiation to the bladder. The 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 a repeat transurethral resection of the site of the original tumor, ultrasound-guided whole-layer biopsy, and urine cytology, as well as magnetic resonance imagery (MRI) and CT scan of the pelvis, and the response to this therapy was then evaluated.

Response

Overall, more than 75% of patients achieved a CR as defined by the absence of persistent disease revealed by cystoscopy, biopsy, and urine cytology after therapy, and more than 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 161 weeks from the completion of therapy.[6] Most of the patients who achieved CR had locally invasive tumors (stage T2 or T3 node-negative) and UC histologically. Figure 3 shows horizontal, coronal and sagittal MRI images obtained before and after treatment of the patients who had lymph node metastasis but achieved CR. In contrast to the high CR induction ratio in patients with locally invasive UC tumors, however, most patients with lymph node involvement (nine of 10 patients; 90%, 95% CI, 55.4–99.7%), stage T4 tumors (13 of 16 patients; 26.8%, 95% CI, 14.2–42.9%), and/or tumors besides UC (one patient with squamous cell carcinoma, one patient with choriocarcinoma, and five patients with adenocarcinoma) failed to achieve CR after the treatment.[6]

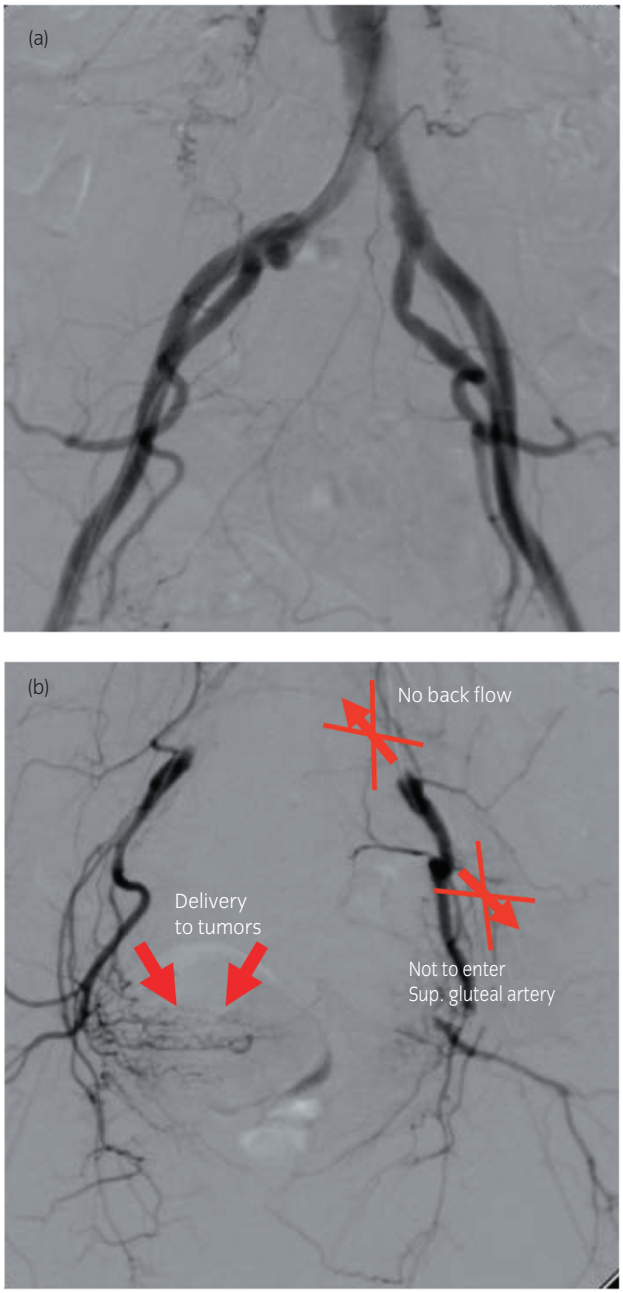

Fig. 2 Bilateral common iliac arteriography before (a) and after (b) balloon occlusion.

Salvage therapy for remaining cancer

Overall, two patients who were found to have only a non-muscle invasive remaining tumor underwent intravesical injection of Bacille Calmette-Guérin (BCG). One patient achieved CR with no evidence of recurrent disease or distant metastasis after a follow-up period of 80 weeks. The other, however, suffered disease progression, necessitating radical cystectomy. We recommended radical cystectomy as a salvage therapy for patients with any remaining invasive tumor without lymph node involvement. However, most

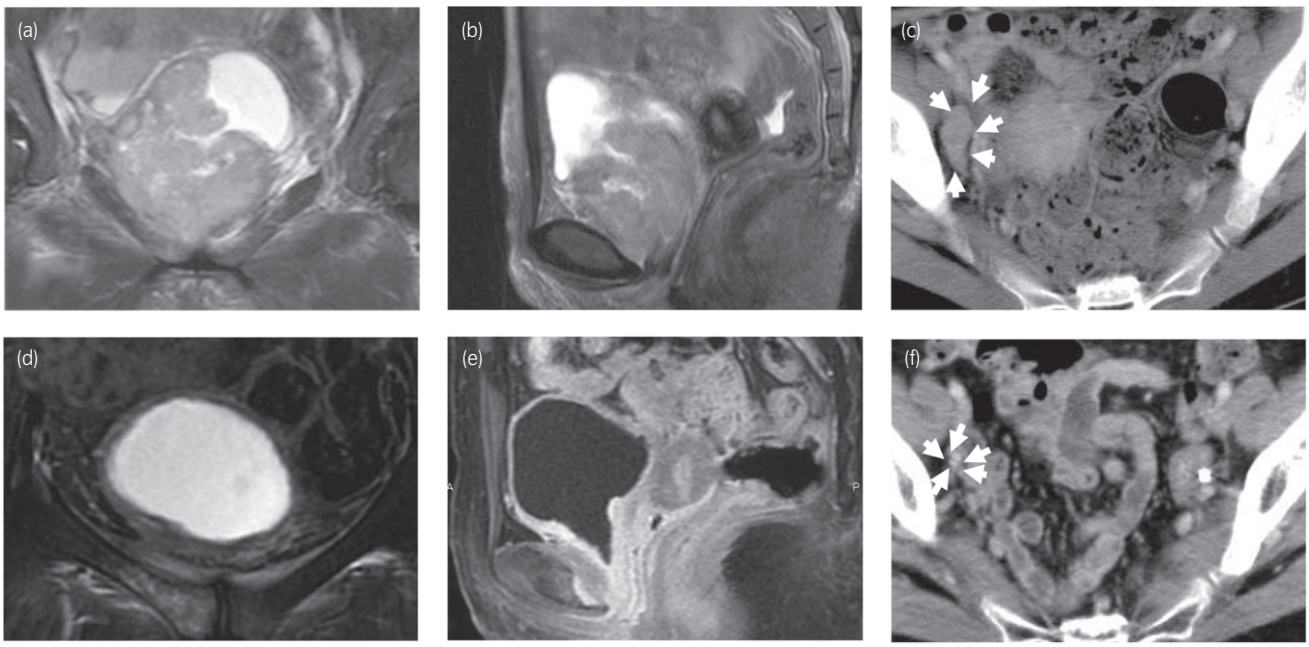

Fig. 3 Magnetic resonance imaging (MRI) before (a, b, c) and after (d , e, f) the treatment. The horizontal (a), coronal (b) and sagittal (c) MRI slices reveal that bulky tumors occupy more than half of the bladder cavity, and that the tumors invade the abdominal wall, indicating stage T4. In contrast, all imaging studies (d , horizontal; e, coronal; and e, sagittal slices) confirm a complete disappearance of the tumors, and that the mucosa and muscle layer are intact at 10 weeks after completion of the therapy.

Table 4 Predictors of overall survival in the Osaka Medical College regimen group evaluated by univariate and multivariate Cox regression analyses

	Category	Univariate		Multivariate	
		Hazard ratio	*P*-value	Hazard ratio	*P*-value
T-stage	T4 *vs* T2-3	14.08	<0.0001	6.803	0.0124
N-stage	N(+) *vs* N(–)	14.49	<0.0001	7.576	0.0052
Pathology	Non-UC *vs* UC	7.092	<0.0001	1.287	0.7576
Performance status	2 *vs* 0–1	2.577	0.0624	1.118	0.8879
Sex	Male *vs* female	1.020	0.9691	1.070	0.9113
Age	Cont. variable	1.038	0.1834	1.037	0.1885
Amount of CDDP	Cont. variable	1.004	0.1511	1.353	0.6223

CDDP, cisplatin; cont. variable, continuous variable; UC, urothelial carcinoma.

patients were ineligible for this option because of their age and performance status or the presence of other disease, such as myocardial infarction and liver dysfunction. These patients received secondary BOAI with gemcitabine (1600 mg), which can also be eliminated by HD, as a salvage therapy, or requested no further treatment. Six patients received secondary BOAI with gemcitabine; one of them achieved CR and two achieved a partial response (PR) with no evidence of recurrent disease or distant metastasis at the 1-year follow-up point, while the other three patients showed progressive disease or disease recurrence after a period of stable disease.[6]

Comparison of survival between the OMC regimen and radical cystectomy

Overall survival was significantly improved in the OMC regimen group. Figure 4a shows the Kaplan–Meier curves used for comparison of OS demonstrating 5-year and 15-year survival rates of 76.3 and 65.4%, respectively (*vs* 59.8 and 40.1% in the cystectomy group, log–rank test, $P < 0.0475$, Fig. 4a). Figure 4b shows Kaplan–Meier curves among the two OMC regimen subgroups (OMC confined, comprising patients with organ confined disease, and OMC T4-N+, comprising patients with stage T4 or N+ disease)

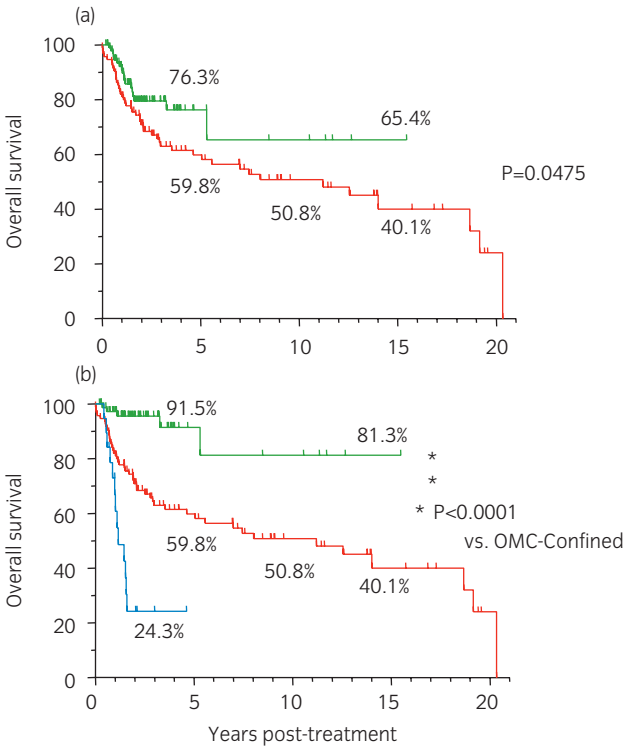

Fig. 4 Kaplan–Meier curves for overall survival in each group comparing overall survival (a) between the Osaka Medical College (OMC) regimen and cystectomy groups, and (b) the two OMC regimen subgroups (OMC confined and OMC T4-N+), and the cystectomy group. The OMC confined group comprised patients with organ confined disease, and the OMC T4-N+ group comprised patients with stage T4 or N(+) disease. (a) —, OMC; —, cystectomy; (b) —, OMC confined; —, OMC T4,N(+); —, cystectomy. In Fig. 4a $P = 0.0475$; in Fig. 4b $P = 0.0001$ versus OMC confined group.

and the cystectomy group. As can be seen, the 5-year and 15-year survival rates were even better, at 91.5 and 81.3%, respectively ($P < 0.0001$ *vs* cystectomy group), when the results were compared under the same conditions by matching the clinical stage, and excluding patients with stage T4 tumors and/or lymph node metastasis from the OMC regimen group.

Predictors of OS in patients receiving the OMC regimen

The significance of factors including pretreatment T-stage, lymph node involvement, tumor pathology (UC *vs* non-UC), patient performance status, sex, age, and the amount of CDDP administered were investigated using the Cox regression model as predictors of OS. As shown in Table 4, stage T4 and lymph node metastasis were selected as significant factors affecting OS in both univariate and multivariate Cox regression analyses, and tumor pathology (non-UC) was selected in the univariate Cox regression analysis. Figure 5 shows the Kaplan–Meier curves for OS of patients at each clinical stage (a) and for each histological type (b), respectively.

Toxicity

The most significant outcome of the OMC regimen was that its related toxicities were markedly less severe than those reported for other protocols, as shown in Table 5. None of the patients suffered Grade III or more severe toxicities. Some patients experienced Grade I blood/bone marrow toxicity. No patients were treated with granulocyte colony-stimulating factor or transfusion of red blood cells. Gastrointestinal toxicity included anorexia in 33 patients (34.4%; 95% CI, 25.0–44.8%), constipation in 16 (16.7%; 95% CI, 9.84–25.6%), diarrhea in 19 (19.8%; 95% CI, 12.4–29.2%), nausea in 29 (29.0%; 95% CI, 21.2–40.4%), and vomiting in 10 (10.4%; 95% CI, 5.11–18.3%), but all symptoms disappeared within 4 days after intra-arterial infusion. Three patients experienced Grade I neuropathy in the peroneal nerve area (3.13%; 95% CI, 0.65–8.86%), and one had Grade II neuropathy (1.04%; 95% CI, 0.03–5.67%). With regard to their renal function, four patients showed an increase of more than 20% in the peak level of serum creatinine 7 days after intra-arterial infusion, but this returned to the previous level after 14 days in all patients. In other patients, however, we found no significant differences in the level of blood urea nitrogen (BUN) or serum creatinine before and after intra-arterial infusion. There were no other adverse reactions such as genitourinary toxicity, radiation cystitis or life-threatening complications.

Cisplatin removal ratio

We measured the concentrations of serum free (protein-unbound) platinum and serum total (protein-unbound + protein-bound) platinum in blood draining from the common iliac veins (before HD) as well as in blood returning to the vena cava (after HD) at 30, 60, and 120 min after initiation of HD. More than 95% of protein-unbound platinum was efficiently removed from the blood by HD while intra-arterial infusion of cisplatin was performed (by 60 min after initiation of BOAI), and the concentration of free platinum decreased to below the detection limit by 120 min after the start of HD (Table 6).[5]

Comment

The most noteworthy feature of this treatment policy is that BOAI can deliver an extremely high concentration of cisplatin to the site of a tumor, and that concomitant blood purification may allow an even higher concentration of cisplatin to remain at the tumor site. Collins compared plain i.v. infusion and plain intra-arterial infusion of the same dose of

Table 5 Toxicity

Toxicity	Grade			Duration		
	Grade 1	Grade 2	Grade 3–4	<3 days	3–7 days	>7 days
	N (%)	*N* (%)	*N* (%)	*N*	*N*	*N*
Blood/bone marrow						
Total	8 (8.3)	0	0	0	7 (7.3)	1 (1.0)
Granulocytopenia	6 (6.3)	0	0	0	5 (5.2)	1 (1.0)
Anemia	8 (8.3)	0	0	0	7 (7.3)	1 (1.0)
Gastrointestinal						
Total	49 (51.0)	0	0	0	0	0
Anorexia	33 (34.4)	0	0	21 (21.9)	12 (12.5)	0
Constipation	16 (16.7)	0	0	9 (9.4)	7 (7.3)	0
Diarrhea	19 (19.8)	0	0	12 (12.5)	7 (7.3)	0
Nausea	29 (30.2)	0	0	23 (24.0)	6 (6.3)	0
Vomiting	10 (10.4)	0	0	7 (7.3)	3 (3.1)	0
Neuropathy	3 (3.1)	1 (1.0)	0	0	0	4 (4.2)

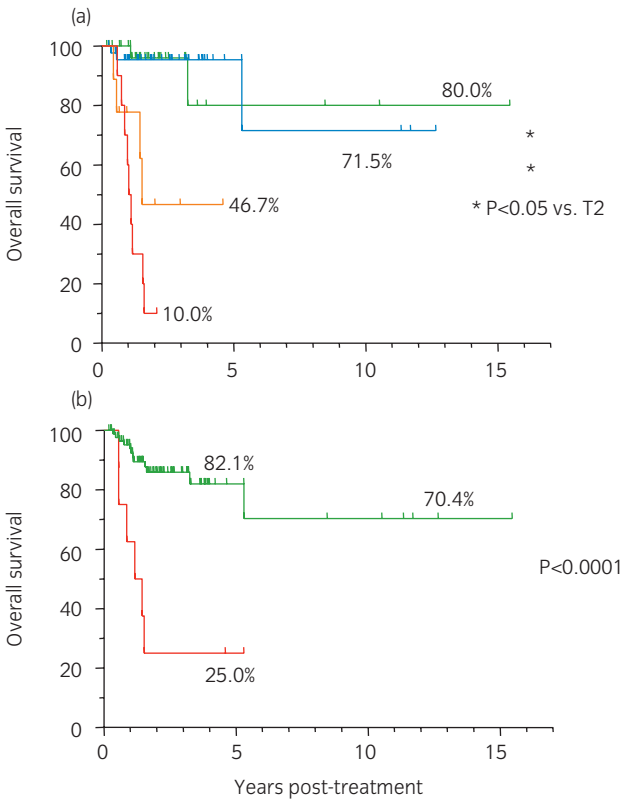

Fig. 5 Kaplan–Meier curves for overall survival of patients treated with the Osaka Medical College regimen at each clinical stage (a) and for each histological type (b), respectively. (a) —, T2; —, T3; —, T4; —, N(+); (b) —, urothelial carcinoma UC; —, non-UC. In Fig. 5a $P = 0.05$ versus T2; in Fig. 5b $P = 0.0001$.

cisplatin and reported that the intratumoral platinum (Pt) concentration was 1.4–5.0 times higher after the latter than after the former.[71] Mitsuzane *et al*. reported that if the tumor-feeding artery was occluded by a balloon, more than sixfold the amount of cisplatin that could be delivered by plain arterial infusion could be accumulated at the site of a tumor.[72] In our previous study, the concentration of cisplatin in blood that had perfused through the vesical region was 8–10 μg/mL after an intra-arterial injection of 300 mg. This plasma concentration implies that the vesical tumor was exposed to a cisplatin perfusate equivalent to a lethal dose 100 percent drug concentration, based on data reported from various studies including phase I clinical trials,[73] animal studies[74] and our own laboratory studies, thus achieving a markedly pronounced cytocidal effect against malignant cells.

In addition to the direct induction of cancer cell death due to 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 cellular death by inhibiting the repair of radiotherapy-induced DNA damage, or it may damage genes known to be related to radiosensitivity, such as BRCA2, and hMLH1, or have both effects, thereby enhancing sensitivity to radiation therapy and eventually leading to apoptosis.[75–77] As several basic research studies have demonstrated that hypoxia markedly enhances cisplatin-induced radiosensitivity,[75,76] the BOAI system, which provides not only a high concentration of cisplatin, but also causes severe

Table 6 Removal ratio of cisplatin by hemodialysis (HD)

Time (min)	Free platinum concentration			Total platinum concentration		
	Pre-HD (μg/mL)	Post-HD (μg/mL)	Removal ratio (%)	Pre-HD (μg/mL)	Post-HD (μg/mL)	Removal ratio (%)
30	2.44 ± 0.28	0.11 ± 0.05	95.3 ± 2.48	4.01 ± 0.55	1.45 ± 0.42	64.1 ± 6.92
60	2.98 ± 0.48	0.13 ± 0.06	95.6 ± 2.42	5.40 ± 0.55	1.97 ± 0.69	64.0 ± 10.7
120	ND	ND	ND	1.79 ± 0.26	1.14 ± 0.23	36.6 ± 7.64

ND indicates below the detection limit.

hypoxia at the tumor site, may also largely contribute to a very efficient anti-tumor effect.

The other noteworthy advantage of this treatment regimen is the significant reduction of systemic side effects. Cisplatin exerts its anti-tumor activity via the non-protein-bound form, which decreases rapidly after administration. Its half-life is normally less than 60 min, decreasing to below the detection limit 4 h after administration.[78,79] Accordingly, the removal of non-protein-bound Pt immediately after the administration of cisplatin, which markedly reduces systemic side effects, may be highly advantageous for patients undergoing selective intra-arterial infusion. In order to accomplish efficient drainage of cisplatin immediately after passage through the tumor, we performed HD via the bilateral common iliac veins. As the molecular weight of protein-unbound cisplatin is approximately 300, similar to that of creatinine, HD can provide extremely marked cisplatin elimination. Additionally, the anatomic structure and blood supply of the bladder may largely account for the efficient drainage of cisplatin with this approach. As the urinary bladder is situated at the base of the pelvis, a large proportion of the cisplatin that has perfused the vesical lumen through the vesical arteries flows into the inferior vena cava via both common iliac veins. Thus, this relatively close circuit formed by the internal iliac artery, bladder, and common iliac veins may contribute to efficient drainage of the anticancer agent, leading to higher elimination efficiency without influencing systemic circulation. Indeed, we found that about 95% of free Pt was efficiently eliminated by HD while the BOAI of cisplatin was performed, and the concentration of free Pt decreased to below detection limit by 120 min after the initiation of HD, thus providing optimal conditions for effective local accumulation in the tumor, with minimal systemic toxicity.

Considering these factors, this method can be regarded as curative therapy targeted mainly at two patient groups: those for whom radical cystectomy is indicated, or patients for whom radical cystectomy is not feasible because of their age or performance status or for other reasons and who are considered physically incapable of tolerating the chemotherapeutic regimens that are usually applied clinically. Thus, it is important to note 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 permit a potentially curative treatment in patients whose condition would normally rule out this likelihood and for whom, otherwise, merely palliative treatment would seem the only option. Our long-term data are too preliminary to allow this treatment regimen to be evaluated as a first-line therapy for locally invasive bladder cancer. Additionally, it is difficult to set an appropriate control group clinically because this therapy is often indicated for patients in the latter group, that is, those for whom radical cystectomy or standard chemotherapy cannot be performed due to advanced age or for other reasons. Nevertheless, all of our patients whose tumors were UC and less than stage T3 achieved CR without tumor recurrence or distant metastasis during a mean follow-up period of 132 weeks. Our results suggest that chemoradiation concomitant with HD is a promising treatment for invasive bladder cancer, particularly stage T3 tumors that are histologically proven to be UC, allowing bladder preservation in both patient groups.

Conflict of interest

None declared.

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