Pathological Complete Response Induced by the Combination Therapy of Gemcitabine and 24-h Infusion of Cisplatin in Two Cases Initially Diagnosed as Node-Positive Advanced Urothelial Carcinomas

Kenji Ina[1*], Ryuichi Furuta[1], Tomoko Nishio[2], Satoshi Kayukawa[3], Takae Kataoka[3], Haruhito Totani[3], Takashi Kanamori[3], Takaki Kikuchi[3], Shun Umeda[4] and Tamio Fujita[4]

[1]Department of Medical Oncology; [2]Department of Pathology, [3]Department of Clinical Oncology; [4]Department of Urology, Nagoya Memorial Hospital, Nagoya, Japan

Abstract: We report on two patients, successfully treated by the combination therapy of gemcitabine and 24-h intravenous infusion of cisplatin, who were initially diagnosed with node-positive advanced urothelial cancer. Each patient had a very good clinical response and underwent curative radical surgery after gemcitabine/cisplatin chemotherapy. A microscopically detailed examination of surgically obtained specimens showed the complete disappearance of malignant cells in the two cases. As a pilot study, we have used the regimen of gemcitabine plus 24-h continuous infusion of cisplatin, instead of bolus injection, for the treatment of 20 patients with node-positive or metastatic urothelial cancer. The clinical response rate in this regimen was 75% (complete response 7/20; 35%, partial response 8/20; 40%). The median overall survival was 665 days. As for the adverse effects, the incidences of severe neutropenia and thrombocytopenia (grade 3-4) were 20% and 15%, which might be less toxic than conventional gemcitabine plus cisplatin therapy. The 24-h infusion of cisplatin combined with gemcitabine can be highly recommended as neoadjuvant chemotherapy for locally advanced urothelial cancer.

Keywords: Urothelial carcinoma, cisplatin, gemcitabine, pathological complete response.

INTRODUCTION

Chemotherapy is the main treatment for node-positive or metastatic urothelial carcinoma [1, 2]. The sensitivity of urothelial cancer to chemotherapy was noted in the 1970s and platinum based regimens such as MVAC (methotrexate, vinblastin, doxorubicin, and cisplatin) resulted in responses consisitently exceeding 50% [3, 4]. Newer agents including taxanes and gemcitabine were found to be active in the 1990s [5, 6]. The reports comparing MVAC with gemcitabine/ cisplatin demonstrated the equivalence of the two regimens [7, 8]. Because it shows the comparable antitumor effects with less toxicity, compared to MVAC regimen, the combination therapy of gemcitabine plus cisplatin is now commonly used as a first line therapy for metastatic urothelial cancer [9]. However, in the neoadjuvant settings, a comprehensive evaluation of this combination therapy is still lacking [10].

Although considerable progress has been made in supportive care and emesis control [11, 12], renal functions of the patients with advanced urothelial cancer are sometimes impaired [13] partly because of the urinary obstruction by tumor invasion. We have used 24-h continuous infusion of cisplatin [14, 15], instead of bolus injection, in combination with gemcitabine for the treatment of node-positive or metastatic urothelial cancer patients, including cisplatin-unfit patients, since 2005.

PATIENTS AND METHODS

Patients were eligible if they signed the informed consent form and met all the following criteria: pathologically proven transitional cell carcinoma (TCC) or clinically diagnosed as node-positive or metastatic urothelial cancer; age 20-85 years; Eastern Cooperative Oncology Group performance status of 0-3; no prior chemotherapy; a white blood cell count between 4,000 and 12,000/mm^3, a platelet count of >10,000/mm^3, and haemoglobin of >8 g/dL; serum bilirubin <1.5 mg/dL, aspirate aminotransferase and alanine aminotransferase <3 times the upper limit of normal (ULN); and estimated GFR (eGFR) > 35 ml/min. Patients with advanced urothelial cancer were treated with bolus injection of gemcitabine (1000 mg/m^2) on day 1, 8, and (15) and 60 mg/m^2 of cisplatin (24-h intravenous infusion) on day 2. Doses of cisplatin were modified based on the renal functions: eGFR > 60 ml/min 60 mg/m^2, 40-60 ml/min 30 mg/m^2, 35-40 ml/min 20 mg/m^2. Response Evaluation Criteria in Solid Tumors (RECIST) and National Cancer Institute common toxicity criteria (NCI-CTC) version 4.0 were applied to evaluate antitumor effects and adverse effects, respectively. Overall survival (OS) was

*Address correspondence to this author at the Department of Medical Oncology, Nagoya Memorial Hospital, 4-305 Hirabari, Tenpaku-ku, Nagoya 468-8520, Japan; Tel: +81-52-804-1111; Fax: +81-52-803-8830;
E-mail: kina@hospy.or.jp

ISSN: 1927-7210 / E-ISSN: 1927-7229/13

calculated from the start of chemotherapy to death or the latest follow-up day. The Kaplan-Meier method was used to plot OS curves.

RESULTS

In this pilot study, we enrolled 20 patients with node-positive or metastatic urothelial cancer from July, 2005 to June, 2013 (Table **1**). The overall response rate was 75% (15/20) (Table **2**). Among them, the pathologically complete response was demonstrated in two cases, which was confirmed by a histologically detailed evaluation of the resected specimens of the primary tumor and surrounding lymph nodes. Grade 3-4 toxicities were neutropenia (20%) and thrombocytopenia (15%) (Table **3a**). As for non-hematological toxicities, three cases (Case 6, 9, 20) stopped due to progress in renal dysfunction and one (Case 14) ceased because of interstitial pneumonia (Table **1**, **2**, and **3b**). The median OS of 20 cases was 665 days (range 141 – 3074 days) (Figure **1**).

Case 1

A 59-year old man admitted because of gross hematuria and acute renal failure (BUN 29 mg/dL, Creatinine 2.24 mg/dL, eGFR 25 ml/min). Computed tomography (CT) scan image showed 60 x 40 mm size mass in the bladder, which caused bilateral urinary tract obstruction, and swollen para-aortic lymph nodes without any distant metastases (T3N2M0) (Figure **2A**). After renal drainage was constructed, renal function was improved (BUN 20 mg/dL, Creatinine 1.39 mg/dL, eGFR 35 ml/min, Creatinine clearance 32 ml/min). And then chemotherapy was initiated on February 28, 2012 and 24-h infusion of cisplatin was performed at a dose of 20 mg/m^2. Grade 3 neutropenia was observed during the chemotherapy and despite of recurrent urinary tract infection renal function was gradually improved to 52 ml/min of creatinine clearance. Consequently, the chemotherapeutic efficacy was diagnosed as partial response (PR) after 3 courses. A reevaluation after 9 courses of this therapy showed only a small elevated lesion in the bladder with no swollen lymph nodes (Figure **2B**). Although the patient was well informed that cystectomy was not curative, he underwent surgery in the hope of cure. We performed radical cystectomy with pelvic lymph node dissection on September 26, 2012. A microscopic examination of the resected specimens revealed the complete disappearance of cancer cells at the site of the primary lesion (Figure **3A**, **B**).

Table 1: Patients' Characteristics

Case number	Age	Gender	TNM classification
1	59	M	T3, N1, M0
2	70	F	T4, N3, M1
3	58	M	T3, N2, M0
4	69	M	metastases (lung)
5	63	M	metastases (lymph nodes)
6	72	M	T4, N1, M0
7	65	M	metastasis (muscle)
8	70	M	T3, N1, M0
9	65	M	metastases (lymph nodes)
10	60	M	T3b, N1, M0
11	58	F	T4a, N1, M0
12	51	M	T4a, N2, M1
13	78	M	T4, N1, M0
14	75	M	T4a, N1, M0
15	62	M	T3, N2, M0
16	76	F	metastasis (intrapelvic mass)
17	57	F	metastasis (intrapelvic mass)
18	59	M	T4, N1, M0
19	62	M	T4, N3, M1
20	68	M	T4a, N2, M1

Table 2: Clinical Responses to Chemotherapy

Case number	Number of cycles	Chemotherapeutic effects	Date of death
1	9	CR	alive
2	11	CR	alive
3	6	CR	alive
4	11	CR	alive
5	8	CR	2011.8.11
6	2	CR	alive
7	10	CR	alive
8	5	PR	alive
9	5	PR	2012.3.29
10	3	PR	alive
11	6	PR	2010.12.27
12	3	PR	2008.7.14
13	9	PR	2010.5.6
14	2	PR	2013.6.20
15	4	PR	alive
16	3	SD	alive
17	5	SD	alive
18	4	SD	2009.6.12
19	3	PD	2006.11.5
20	2	PD	2007.9.19

CR: complete response, PR: partial response, SD: stable disease, and PD: progressive disease.

Table 3a: Hematological Adverse Effects

Grade	1	2	3	4
Neutropenia	1	9	4	0
Thrombocytopenia	5	4	3	0

Table 3b: Non-Hematological Adverse Effects

Renal dysfunction		3		
eGFR	before	47	45	40
	after	32	26	25
Others	Interstitial pneumonia	1		

Case 6

A 72-year old man consulted our hospital because of gross hematuria. Magnetic resonance image (MRI) showed the left ureteral tumor (20 x 30 mm) with bladder invasion and lymph node enlargement in the internal iliac region (Figure **4A**). Endoscopic biospsy samples showed TCC with grade 2 (Figure **5A**). As a provisional diagnosis of T4N1M0, combination therapy of gemcitabine and cisplatin was started on August 30, 2012. The dose of cisplatin was reduced to 30 mg/m^2, because eGFR was less than 60 ml/min. Cisplatin was dissolved into 1000 ml of saline and then continuously infused for 24-h. After two courses of this chemotherapy, eGFR was further decreased to 32

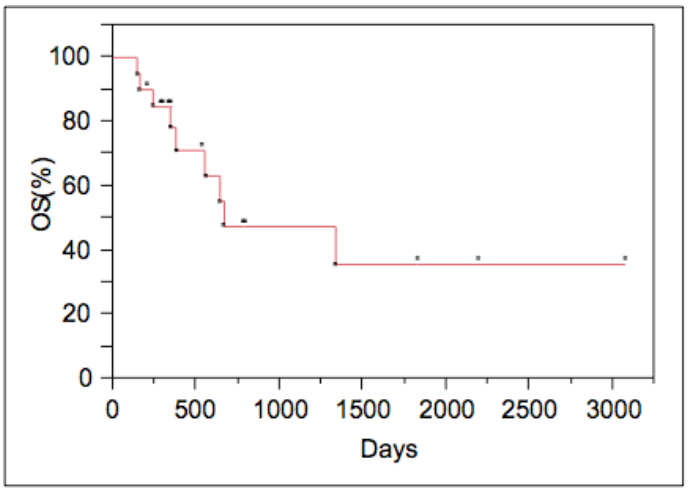

Figure 1: Kaplan-Meier curves of overall survival (OS).

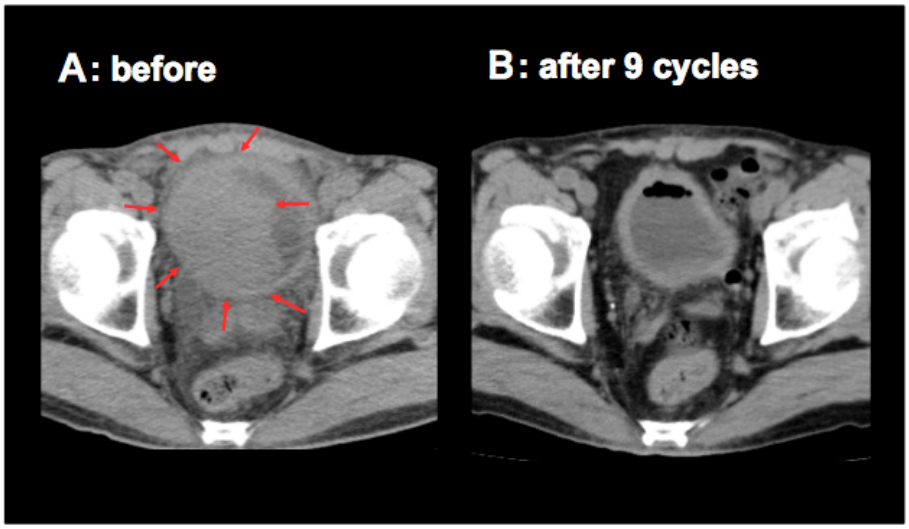

Figure 2: Computed tomography (CT) scans demonstrated a huge mass in the bladder (arrow) (**A**). Only a small elevated lesion was observed in the bladder after 9 cycles of chemotherapy (**B**).

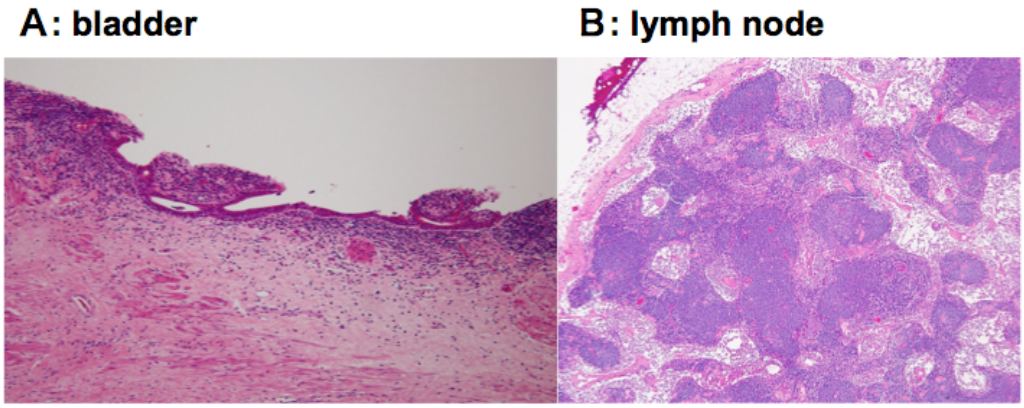

Figure 3: Microscopically, no malignant cells were observed in the bladder (**A**) nor the regional lymph nodes (**B**).

ml/min and, therefore, cisplatin was replaced by oxaliplatin. Another 4 courses of chemotherapy were administered and then MRI showed complete response (CR) (Figure **4B**) and cystoscopic examination showed a disappearance of malignant tumors. Radical Surgery was performed on February 6, 2013. A microscopic

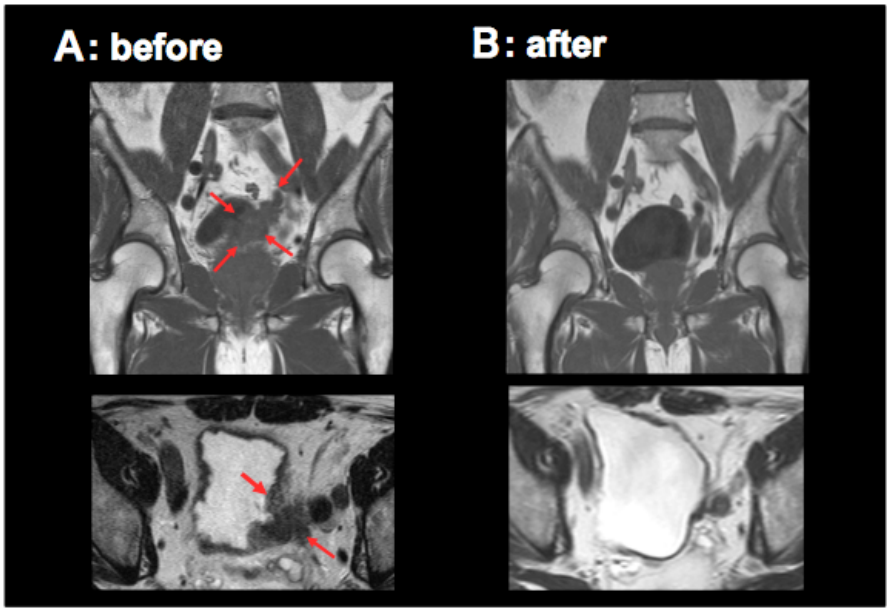

Figure 4: Magnetic resonance image (MRI) showed the left urethral duct tumor (20 x 30 mm) with bladder invasion and lymph node enlargement in the internal iliac region (A). Complete disppearance of the primary tumor and enlarged lymph nodes was demonstrated after platinum-based chemotherapy.

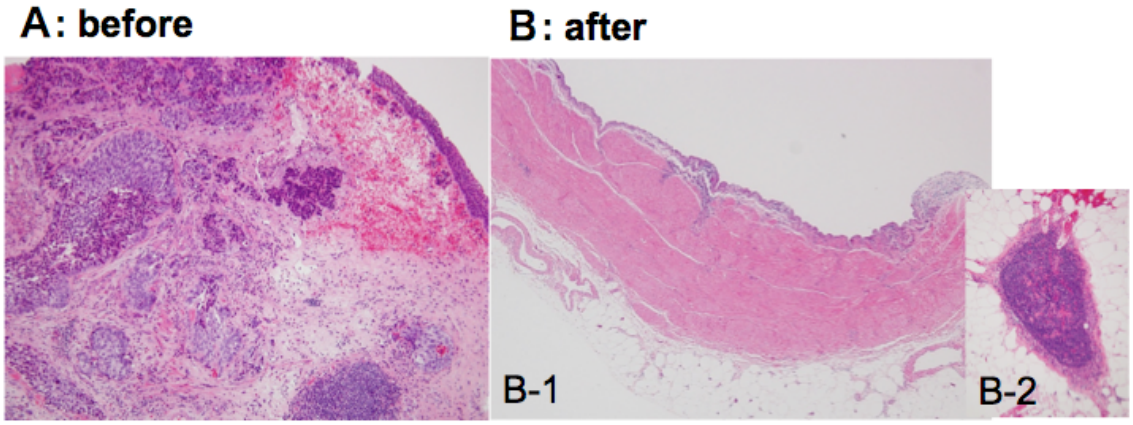

Figure 5: A: Before the initiation of chemotherapy, endoscopic biospsy samples showed transitional cell carcinoma (TCC) with grade 2.

B: A detailed histological examination of surgically resected specimens showed that no malignant cells were observed at the site of the primary lesion (B-1) and regional lymph nodes (B-2).

examination using multiple sections of the resected primary lesions and lymph nodes showed a pathological CR (Figure **5B**).

CONCLUSIONS

The clinical response rate in our regimen using a 24-h continuous infusion of cisplatin combined with gemcitabine was 75% (CR 7/20; 35%, PR 8/20; 40%). In this pilot study, the median OS of our 20 cases was 665 days [16-19]. Table **4** presents the results of our study in comparison with currently accepted first-line regimens containing gemcitabine for the treatment of advanced urothelial cancer. The recent randomized phase III trial showed that triple combination of cisplatin, gemcitabine, and paclitaxel provided a higher response rate than the combination of gemcitabine plus cisplatin (55.5% versus 43.6%), however, survival benefit did not reach statistical difference (median OS 15.8 months versus 12.7 months) [16]. Considering the results of this randomized study, chemotherapeutic activities of our regimen should be comparable, although the number of cases in our pilot study was very small.

With regard to adverse effects, the incidences of severe (grade 3-4) neutropenia and thrombocytopenia were 20.0% and 15.0%, respectively, which

Table 4: First-Line Chemotherapy Using Gemcitabine in Advanced Urothelial Carcinoma

Ref.	N	Agent	Dose	IV	Day	Days/cycle	RR	Side effects(%)	
			(mg/m^2)				(%)	(a)	(b)
[7]	203	gemcitabine	1000	30 min	1, 8, 15	28	49.0	71.0	57.0
		cisplatin	70	bolus	2				
[16]	314	gemcitabine	1000	30 min	1, 8, 15	28	43.6	50.5	52.1
		cisplatin	70	bolus	2				
	312	gemcitabine	1000	30 min	1, 8	21	55.5	64.3	34.5
		cisplatin	70	bolus	2				
		paclitaxel	80	60 min	1, 8				
[17]	38	gemcitabine	2500	30 min	1, 15	28	39.0	50.5	52.1
		cisplatin	35	bolus	1, 15				
[18]	119	gemcitabine	1000	30 min	1, 15	28	41.2	52.5	48.3
		carboplatin	4.5x[GFR+25]	1-h	1, 15				
[19]	18	gemcitabine	1200	30 min	1, 14	28	36.0	11.8	35.3
		oxaliplatin	100	bolus	1, 14				
Our data	20	gemcitabine	1000	30 min	1, 8, (15)	21(28)	75.0	20.0	15.0
		cisplatin	20-60	24-h	2				

N: number of cases, IV: intravenous infusion, RR: response rate.
(a) Neutropenia (grade 3/ 4).
(b) Thrombocytopenia (grade 3/ 4).

might be less toxic than conventional combination therapy of gemcitabine plus cisplatin [7, 16, 20]. On the contrary, renal toxicities were observed in 15.0% (3/20), whose incidence was rather high [7, 16, 21]. It is mainly because our study included the patients with poor renal functions (eGFR < 40 ml/min 2 cases; 40-60 ml/min 6 cases) as well as cisplatin-fit patients (eGFR > 60 ml/min 12 cases). We reduced the dose of cisplatin according to their renal functions, however, we repeated chemotherapy as much as possible (cycle numbers 2-11). Accordingly, twelve patients received more than 5 cycles of chemotherapy and the response rate was comparable to the previous reports [7, 16]. As a result three out of 15 responders to this combination therapy were successfully treated with surgery and two of them revealed a pathological CR. A histologically detailed examination of their resected specimens showed complete disappearance of cancer cells, therefore, no postoperative adjuvant therapy was performed [22, 23]. These two cases are free of recurrence at 23 and 7 months after the surgical resection and at 31 and 24 months after the initiation of the combination therapy, respectively.

In conclusion, the combined therapy of 24-h infusion of cisplatin with gemcitabine is considered to be active and well-tolerated regimen even for the cisplatin-unfit patients with urothelial carcinoma, although the dose reduction of cisplatin may be needed.

SUPPORTING FOUNDATIONS

No funding was received.

REFERENCES

[1] Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. J Urology 2005; 174: 14-20. http://dx.doi.org/10.1097/01.ju.0000162039.38023.5f

[2] Costaniti C, Millard F. Update on chemotherapy in the treatment of urothelial carcinoma. The Scientific World J 2011; 11: 1981-94. http://dx.doi.org/10.1100/2011/590175

[3] Sternberg CN, Yagoda A, Scher HI, *et al.* Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium: efficacy and patterns of response and relapse. Cancer 1989; 64: 2448-58. http://dx.doi.org/10.1002/1097-0142(19891215)64:12<2448::AID-CNCR2820641209>3.0.CO;2-7

[4] Loehrer PJ Sr, Einhorn LH, Elson PJ, *et al.* A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: A cooperative group study. J Clin Oncol 1992; 10: 1066-73.

[5] McCaffrey JA, Hilton S, Mazumdar M, *et al.* Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997; 15: 1853-57.

[6] Lorusso V, Pollera CF, Antimi M, *et al*. A phase II study of gemcitabine in patients with transitional-cell carcinoma of the urinary tract previously treated with platinum. Eur J Cancer 1998; 34: 1208-12. http://dx.doi.org/10.1016/S0959-8049(98)00030-6

[7] Von Der Maase H, Hansen SW, Roberts JT, *et al*. Cemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicine, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000; 18: 3068-77.

[8] Von Der Maase H, Sengelov L, Roberts JT, *et al*. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicine, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005; 23: 4602-608. http://dx.doi.org/10.1200/JCO.2005.07.757

[9] Tanji N, Ozawa A, Miwa N, *et al.* Long-term results of combined chemotherapy with gemcitabine and cisplatin for metastatic urothelial carcinomas. Int J Clin Oncol 2010; 15: 369-75. http://dx.doi.org/10.1007/s10147-010-0069-2

[10] Dash A, Pettus JA, Hansel DE, *et al.* A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008; 113: 2471-77. http://dx.doi.org/10.1002/cncr.23848

[11] Sternberg CN, de Mulder PH, Schornagei JH, *et al.* Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors. J Clin Oncol 2001; 19: 2638-46.

[12] Grumberg S, Chua D, Maru A, *et al.* Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol-EASE. J Clin Oncol 2011; 29: 1495-501. http://dx.doi.org/10.1200/JCO.2010.31.7859

[13] Galsky MD, Hahn NM, Rosenberg G, *et al.* Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011; 14: 2432-38. http://dx.doi.org/10.1200/JCO.2011.34.8433

[14] Iwase H, Shimada M, Tsuzuki T, *et al.* A phase II multi-study of triple therapy with paclitaxel, S-1, and cisplatin in patients with advanced gastric cancer. Oncology 2011; 80: 76-83. http://dx.doi.org/10.1159/000328746

[15] Ina K, Kataoka T, Takeuchi Y, *et al.* Pathological complete response induced by combination therapy of S-1 and 24-hour infusion of cisplatin in two cases initially diagnosed as inoperable highly advanced gastric cancer. Oncology Reports 2008; 20: 259-64.

[16] Bellmunt J, von Der Maase H, Mead GM, *et al.* Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gmcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC intergroup study 30987. J Clin Oncol 2012; 30: 1107-13. http://dx.doi.org/10.1200/JCO.2011.38.6979

[17] Morales-Barrera R, Bellmunt J, Suarez C, *et al.* Cisplatin and gemcitabine administered every two weeks in patients with locally advanced or metastatic urothelial carcinoma and impaired renal function. Eur J Cancer 2012; 48: 1816-21. http://dx.doi.org/10.1016/j.ejca.2012.04.002

[18] Santis MD, Bellmunt J, Mead G, *et al.* Randomized phase II/ III trial assessing gemcitabine/ carboplatin and methotrexate/ carboplatin/ vinblatine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012; 30: 191-99. http://dx.doi.org/10.1200/JCO.2011.37.3571

[19] Eroglu Z, Fruehauf JP. A phase II study of gemcitabine and oxaliplatin in advanced transitional cell carcinoma of the bladder. Cancer Chemother Pharmacol 2013; 72: 263-67. http://dx.doi.org/10.1007/s00280-013-2178-x

[20] Moore MJ, Winquist EW, Murray N, *et al.* Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1999; 17: 2876-81.

[21] Von Der Maase H, Anderson L, Crino S, Weinknecht S, Dogliotti L. Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urothelium: a phase II clinical trial. Ann Oncol 1999; 10: 1461-65. http://dx.doi.org/10.1023/A:1008331111654

[22] Fairey AS, Daneshmand S, Quinn D, *et al.* Neoadjuvant chemotherapy with gemcitabine/cisplatin vs. methotrexate/ vinblastine/doxorubicin/ cisplatin for muscle-invasive urothelial carcinoma of the bladder: a retrospective analysis from the University of Southern California. Urologic Oncol 2012; 1-7.

[23] Yuh BE, Ruel N, Wilson TG, Vogelzang N, Pal SK. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol 2013; 189: 1682-86. http://dx.doi.org/10.1016/j.juro.2012.10.120

Received on 09-09-2013 Accepted on 22-10-2013 Published on 08-11-2013

http://dx.doi.org/10.6000/1927-7229.2013.02.04.1