Case Report

Cisplatin and S-1 for urachal carcinoma: A single-institution case series

Tetsuya Urasaki,[1] Yoichi Naito,[1,2,3] Nobuaki Matsubara,[1,4] Masaoki Sasaki,[1] Takahiro Kogawa[1,2] and Ako Hosono[1,3]

[1]Department of Breast and Medical Oncology, National Cancer Center Hospital East, [2]Division of Experimental Therapeutics, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Chiba, [3]Rare Cancer Center, National Cancer Center, Tokyo, and [4]Department of Urology, National Cancer Center Hospital East, Chiba, Japan

Abbreviations & Acronyms
5-FU = 5-fluorouracil
CA = carbohydrate antigen
CDDP = cisplatin
CI = confidence interval
CR = complete response
EGFR = epidermal growth factor receptor
GC = gemcitabine and cisplatin
Gem-FLP = 5-FU, leucovorin, gemcitabine and cisplatin
IFEP = ifosfamide, 5-FU, etoposide, and cisplatin
IFL = irinotecan, 5-FU, and leucovorin
IRIS = irinotecan and S-1
ITP = ifosfamide, paclitaxel, and cisplatin
LN = lymph node
MVAC = methotrexate, vinblastine, adriamycin, and cisplatin
OS = overall survival
PD = progressive disease
PFS = progression-free survival
PR = partial response
SD = stable disease

Correspondence: Yoichi Naito M.D., Department of Breast and Medical Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa City, Chiba 277-8577, Japan. Email: ynaito@east.ncc.go.jp

Received 31 January 2019; accepted 10 March 2019. Online publication 9 April 2019

Introduction: Urachal carcinoma is a rare cancer, manifesting predominantly as adenocarcinoma, and could be treated with chemotherapy in patients with advanced or recurrent disease. However, any standard chemotherapy regimens are yet to be determined.

Case presentation: We retrospectively reviewed five patients with urachal adenocarcinoma treated with a potent first-line chemotherapy, cisplatin and S-1, between 2011 and 2014. Among the five patients, three were males. The median age at diagnosis was 61 years, ranging from 47 to 67. The most common symptom at their first visit was macroscopic hematuria. The best response was stable disease in four patients, which persisted for 7 months. Three patients experienced only one episode of grade 3 toxicity. Cisplatin and S-1 was well tolerated and safe.

Conclusion: The activity of cisplatin and S-1 is modest and more efficacious treatment is desired against urachal carcinoma.

Key words: chemotherapy, cisplatin, S-1, urachal carcinoma.

Keynote message

The combination of CDDP + S-1 is a potent first-line chemotherapy regimen for patients with advanced or recurrent urachal cancer. We reviewed the cases of five patients who received CDDP + S-1 chemotherapy. CDDP + S-1 confers modest activity in these patients.

Introduction

Urachal carcinoma is one of the rare malignancies because of its frequency of occurrence and poor results with clinical research. In locally advanced urachal carcinoma, curative surgical treatment is recommended. However, in the recurrent or metastatic disease, any standard chemotherapy regimens have not been established yet.

The 5-year survival rate of patients with urachal carcinoma is <50%, which is poorer than the average cancer survival rate;[1,2] this is because no standard chemotherapy regimen is available for the patients thus far. Some groups have used CDDP-based chemotherapy regimens for bladder carcinoma, but both MVAC and GC regimens have been insufficient to control the malignancy,[1,3] while ITP regimen for urothelial tracts showed that one of six patients with urachal carcinoma achieved CR.[4] Meanwhile, the immunohistochemical profile of urachal adenocarcinoma is similar to that of colorectal adenocarcinoma; CK20 and CDX2 are usually positive in both types, while CK7 positivity is variable.[5] Moreover, similar to colorectal adenocarcinoma, urachal adenocarcinoma could also have microsatellite instability and KRAS mutations.[6] Currently, many clinical groups use the chemotherapy regimens for colon carcinomas in treating urachal carcinoma patients: IFL, modified FOLFOX6, and IRIS.[7–9]

Siefker-Radtke *et al.* have reported effective outcomes with several chemotherapy regimens including both 5-FU and CDDP.[1] At the MD Anderson Cancer Center, investigators

Table 1 Characteristics of five patients with urachal carcinoma treated with CDDP + S-1 chemotherapy

Characteristics	No. of patients
Sex	
Male/female	3/2
Age at diagnosis	
<55 years/55 years or more	2/3
Symptoms and signs	
Macroscopic hematuria/micturition pain/upper abdominal pain	3/1/1
Sheldon tumor stage	
IIIA/IVA/IVB	3/1/1
Mayo tumor stage	
II/III/IV	3/1/1
Histology	
Adenocarcinoma: mucinous type/mixed type/not otherwise specified	5: 3/1/1
Cystectomy	
Partial/radical/no	4/0/1
LN dissection	
Yes/no	3/2
Chemotherapy	
For metastatic disease/salvage (for recurrence)	1/4
Tumor marker†	
Carcinoembryonic antigen/CA19-9/CA125/none	4/1/1/1
Family history of cancer	
Colon cancer/other cancers/none	2/3/0
Metastatic/recurrent site	
LN/lung/peritoneum/liver/bone	3/2/1/1/1
Smoking	
Heavy smoker (>30 pack-years)/light smoker (≤30 pack-years)/non-smoker	2/1/2
Drinking	
Regular drinker/occasional drinker/non-drinker	3/1/1

†One patient showed elevated serum level of all three markers.

implemented a phase II trial of Gem-FLP originally for adenocarcinomas of the urothelial tract and urachal remnant.[10,11] The IFEP regimen, originally for advanced bladder cancer, was also applied to patients with urachal carcinoma.[12] It is essential that the S-1 plus CDDP combination chemotherapy is the standard first-line treatment for patients with advanced gastric cancer.[13] Also, CDDP + S-1 chemotherapy regimen has been reported to have some presumptive advantage in patients with urachal adenocarcinoma.[12,14] In the present study, we retrospectively analyzed the clinical outcomes of patients with urachal adenocarcinoma treated with CDDP + S-1 chemotherapy in our institution.

Case presentation

This study was approved by the Institutional Review Board of the National Cancer Center of Japan. Patients were eligible if they had confirmed adenocarcinoma of urachal origin, as determined histologically and by imaging. We retrospectively reviewed five patients who had been treated with CDDP + S-1 first-line chemotherapy regimen in our institution from June 2011 to March 2014.

The dosage and administration schedule of S-1 + CDDP were according to that in a previous report.[13] S-1, an oral 5-FU derivative consisting of tegafur, gimeracil, and oteracil potassium, was administered orally at a dose of 80 mg/m^2 per day for 21 consecutive days, followed by 14-day rest. CDDP was administered intravenously for over 2 h at a dose of 60 mg/m^2 per day on Day 8 of each cycle. Treatment was repeated every 35 days up to a maximum of six cycles or unless disease progression was observed.

The diagnosis of urachal carcinoma was based on the MD Anderson Cancer Center criteria.[15] Clinical, laboratory, radiographic, therapeutic, and pathologic data for each individual were retrieved from medical records. Tumors were staged by both the Sheldon and Mayo staging systems.[2,16] Imaging data were reviewed according to the Response Evaluation Criteria in Solid Tumors version 1.1 criteria,[17] and classified as CR, PR, SD, or PD.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events v4.0. All statistical assessments were performed using the statistical package IBM SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

Cohort characteristics

Five patients with urachal adenocarcinoma received treatment with CDDP + S-1. Clinical characteristics of the patients are shown in Table 1.

Response and patient outcomes

Case summaries of all five patients with urachal adenocarcinoma, treated with CDDP + S-1 chemotherapy, are shown in Table 2. Four patients achieved SD and the other had PD, while no patients achieved either CR or PR. Only one patient completed six cycles of CDDP + S-1 chemotherapy. The disease control rate (proportion of patients with best response of CR or PR or SD) was 80%. For PFS and OS, the survival curves were estimated using the Kaplan–Meier method. Our case series demonstrates a median PFS and OS were 7.0 months (95% CI 2.5, 11.5) and 22.4 months (95% CI 0.0, 45.6), respectively (Fig. 1).

Toxicity

The adverse events are shown in Table 3. Of the five patients, three experienced one episode of grade 3 toxicity. There were no therapy-related deaths.

Discussion

This study is a single-institution case series of patients with urachal adenocarcinoma treated with CDDP + S-1 chemotherapy.

The efficacy of CDDP + S-1 chemotherapy has been previously reported in a patient with recurrent urachal carcinoma.[14] The combination of S-1 + CDDP has been considered one of the most promising chemotherapy regimens against urachal adenocarcinoma. In a recent study, CDDP + S-1 regimen showed that two of six patients with

Table 2 Case summaries of five patients with urachal carcinoma treated by CDDP + S-1 chemotherapy

No.	Age/sex	Chief complaint	Histology (adenocarcinoma)	Stage		Status	Surgery	Eastern Cooperative Oncology Group performance status	S-1/CDDP (cycles)	Best overall response
				Sheldon[16]	Mayo[2]					
1	67/male	Macroscopic hematuria	With signet-ring cell carcinoma (mucin-producing)	IIIA → IVB (LN, bone)	II → IV	Recurrent	*En bloc* segmental resection	1	2	SD
2	63/male	Macroscopic hematuria	Poorly differentiated	IVA (LN)	III	Recurrent	*En bloc* segmental resection with pelvic lymph node dissection	0	4	SD
3	53/male	Upper abdominal pain	Well differentiated (mucin-producing)	IVB (LN, lung, liver)	IV	Advanced	Not performed (inoperable)	0	1	PD
4	47/female	Micturition pain	Well to moderately differentiated tubular (mucin-producing)	IIIA → IIIC	II → IV (peritoneal dissemination)	Recurrent	*En bloc* segmental resection with bilateral lymphadenectomy Excision of the recurrent tumors and abdominal wall reconstruction using a right anterolateral thigh flap	0	2	SD
5	61/female	Macroscopic hematuria	Well to moderately differentiated	IIIA → IVB	II → IV (lung)	Recurrent	Laparoscopic *en bloc* partial cystectomy with bilateral lymphadenectomy	0	6	SD

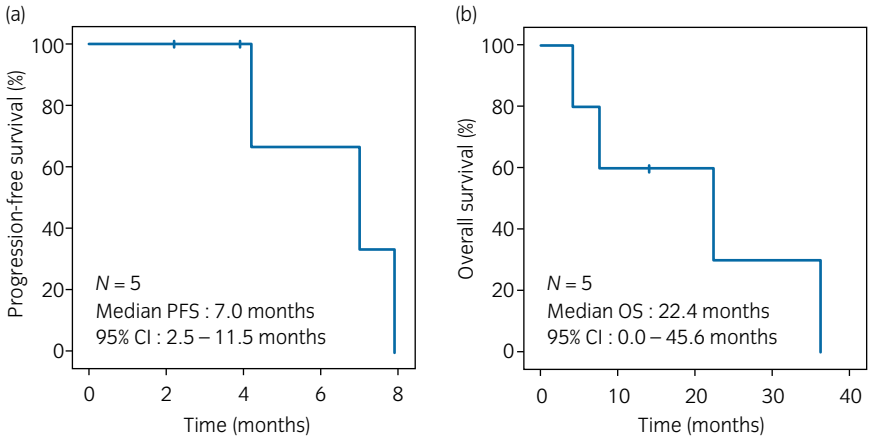

Fig. 1 Kaplan–Meier curves of (a) PFS and (b) OS.

Table 3 Major adverse events that occurred in five patients with urachal carcinoma treated with CDDP + S-1 chemotherapy

	No. of patients	
Adverse event	All grades	Grade ≥3
Hematological		
Thrombocytopenia	3	0
Leukocytopenia	3	0
Anemia	2	1
Neutropenia	1	0
Non-hematological		
Constipation	3	0
Increased alkaline phosphatase level	3	0
Hyperglycemia	3	0
Hypoalbuminemia	3	0
Hypertension	1	1
Thromboembolic event	1	1
Total	58†	3

†The number includes the cases omitted from this table.

urachal carcinoma achieved PR.[12] To date, CDDP + S-1 did not show any obvious safety problems in patients with urachal carcinoma.[12,14] The combination chemotherapy was also well tolerated in our study. Meanwhile, our study showed modest outcome in urachal carcinoma patients treated with CDDP + S-1 chemotherapy. The low response rate of our study suggests the necessity of more active treatment for urachal carcinoma. Currently, the molecular-targeted therapy has been employed widely across the tumor type. Such approach should be integrated into the treatment of urachal carcinoma. A recent report showed that a patient with metastatic wild-type KRAS urachal cancer responded well to cetuximab, a chimeric mouse-human monoclonal antibody targeting the human EGFR.[18] In considering anti-EGFR antibody therapy, patients with urachal adenocarcinoma should be tested for the presence of KRAS and BRAF mutations prior to therapy.[19]

The major limitations of our study include the retrospective design, the small study cohort derived from a single institution, and rarity of the disease. Larger sample sizes could help determine the feasibility of the chemotherapy regimen, but patients with rare tumors may show similar treatment responses.

In conclusion, we reviewed the cases of five patients with urachal adenocarcinoma who received CDDP + S-1 chemotherapy. CDDP + S-1 confers modest activity for patients with advanced or recurrent urachal carcinoma, as indicated from the findings of previous reports and our study. To improve outcomes for urachal carcinoma patients, more efficacious treatment will be needed in the future.

Conflict of interest

The authors declare no conflict of interest.

References

1 Siefker-Radtke AO, Gee J, Shen Y *et al.* Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. *J. Urol.* 2003; **169**: 1295–8.
2 Ashley RA, Inman BA, Sebo TJ *et al.* Urachal carcinoma: clinicopathologic features and long-term outcomes of an aggressive malignancy. *Cancer* 2006; **107**: 712–20.
3 Miyata Y, Sagara Y, Matsuo T *et al.* Response of recurrent urachal cancer to gemcitabine and cisplatin therapy: a case report and literature review. *Anticancer Res.* 2011; **31**: 2335–8.
4 Galsky MD, Iasonos A, Mironov S *et al.* Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. *Urology* 2007; **69**: 255–9.
5 Gopalan A, Sharp DS, Fine SW *et al.* Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. *Am. J. Surg. Pathol.* 2009; **33**: 659–68.
6 Sirintrapun SJ, Ward M, Woo J, Cimic A. High-stage urachal adenocarcinoma can be associated with microsatellite instability and KRAS mutations. *Hum. Pathol.* 2014; **45**: 327–30.
7 Mohile SG, Schleicher L, Petrylak DP. Treatment of metastatic urachal carcinoma in an elderly woman. *Nat. Clin. Pract. Oncol.* 2008; **5**: 55–8.
8 Yazawa S, Kikuchi E, Takeda T *et al.* Surgical and chemotherapeutic options for urachal carcinoma: report of ten cases and literature review. *Urol. Int.* 2012; **88**: 209–14.
9 Yanagihara Y, Tanji N, Miura N *et al.* Modified FOLFOX6 chemotherapy in patients with metastatic urachal cancer. *Chemotherapy* 2013; **59**: 402–6.
10 Siefker-Radtke A. Urachal adenocarcinoma: a clinician's guide for treatment. *Semin. Oncol.* 2012; **39**: 619–24.
11 Siefker-Radtke AO, Dinney CP, Shen Y *et al.* A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urotherial cancer: final results. *Cancer* 2013; **119**: 540–7.

12 Hayashi T, Yuasa T, Uehara S *et al.* Clinical outcome of urachal cancer in Japanese patients. *Int. J. Clin. Oncol.* 2016; **21**: 133–8.
13 Koizumi W, Narahara H, Hara T *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008; **9**: 215–21.
14 Kojima Y, Yamada Y, Kamisawa H *et al.* Complete response of a recurrent advanced urachal carcinoma treated by S-1/cisplatin combination chemotherapy. *Int. J. Urol.* 2006; **13**: 1123–5.
15 Siefker-Radtke A. Urachal carcinoma: surgical and chemotherapeutic options. *Expert Rev. Anticancer Ther.* 2006; **6**: 1715–21.
16 Sheldon CA, Clayman RV, Gonzalez R, Williams RD, Frailey EE. Malignant urachal lesions. *J. Urol.* 1984; **131**: 1–8.
17 Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 2009; **45**: 228–47.
18 Collazo-Lorduy A, Castillo-Martin M, Wang L *et al.* Urachal carcinoma shares genomic alterations with colorectal carcinoma and may respond to epidermal growth factor inhibition. *Eur. Urol.* 2016; **70**: 771–5.
19 Módos O, Reis H, Niedworok C *et al.* Mutations of KRAS, NRAS, BRAF, EGFR, and PIK3CA genes in urachal carcinoma: occurrence and prognostic significance. *Oncotarget* 2016; **7**: 39293–301.