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ORIGINAL ARTICLE

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Combination chemotherapy with ifosfamide, 5-fluorouracil, etoposide and cisplatin for metastatic urothelial cancer

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Abstract *Purpose*: To investigate the activity of combination chemotherapy with ifosfamide, 5-fluorouracil, etoposide and cisplatin in patients with metastatic urothelial cancer. *Methods*: A group of 29 patients were treated with 2000 mg/m^2 ifosfamide, 750 mg/m^2 5-fluorouracil, 100 mg/m^2 etoposide and 20 mg/m^2 cisplatin. All four drugs were given intravenously on days 1 through 3 and the treatment was repeated every 3 weeks. Of the 29 patients, 14 had lymph node metastasis alone, and 15 had visceral lesions. *Results*: An objective response was achieved in 17 patients (59%). There was no difference in response rates according to metastatic site including osseous lesions, which responded well in four of six patients. The 3-year survival rate for all patients was 16% with four patients who had undergone salvage surgery being alive with no evidence of disease 15 to 61 months after initiation of the treatment. A good performance status, lymph node metastasis alone and administration of chemotherapy at the full dosage had a significantly favorable impact on patient survival. Bone marrow toxicity was significant and one patient died of treatment-related sepsis. *Conclusions*: Ifosfamide, 5-fluorouracil, etoposide and cisplatin combination chemotherapy appeared to be active in the treatment of metastatic urothelial cancer. Although bone marrow toxicity was significant, the treatment was well tolerated by the majority of the patients. Further study may be warranted.

Keywords Metastatic urothelial cancer · IFEP chemotherapy · Treatment results

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Introduction

Urothelial cancer is considered a chemosensitive tumor [11]. To date, many clinical trials with various chemotherapy regimens have been performed for the treatment of urothelial cancers. Among them, M-VAC chemotherapy is known to be active and is now widely used [1, 8, 14, 15]. Although the initial response rate is relatively high, the response duration is generally short and the treatment schedule is somewhat complicated. Therefore, we investigated a new combination chemotherapy consisting of cisplatin and three other agents, i.e. ifosfamide, 5-fluorouracil (5-FU) and etoposide, all of which appear to show therapeutic synergism against animal tumors when used in combination with cisplatin [13]. We report here the results of a longer follow-up than that of the preliminary report in patients with metastatic urothelial cancer treated with the chemotherapy [4].

Materials and methods

Patients with a bidimensionally measurable metastatic lesion of urothelial cancer (N2–3 and/or M1) were entered into the study. Patients with performance status of 4, inadequate bone marrow function (WBC $<3500/\mu l$, platelet $<100{,}000/\mu l$), hepatic dysfunction (bilirubin >2.0 mg/dl) or renal dysfunction (creatinine clearance <30 ml/min. or serum creatinine >3.0 mg/dl) were ineligible.

The chemotherapy consisted of 2000 mg/m^2 ifosfamide, 750 mg/m^2 5-FU, 100 mg/m^2 etoposide and 20 mg/m^2 cisplatin (IFEP). On days 1 through 3, each agent was administered intravenously with forced intravenous hydration of 3000 ml/day with mannitol. In cases of overhydration with a weight gain of 3 kg or more, furosemide was also given. 5-FU was administered by 24-h continuous infusion. Antiemetic ($5HT_3$ receptor antagonist) was given 30 min before starting chemotherapy, and 400 mg mesna was also given immediately after, and 4 h and 8 h after infusion of ifosfamide. Granulocyte colony-stimulating factor was administered when the WBC count decreased to less than $2000/\mu l$ and platelet infusion was performed when the platelet count decreased to less than $25{,}000/\mu l$. The treatment was repeated every 3 weeks when the WBC and platelet counts had recovered to $>3000/\mu l$ and $>100{,}000/\mu l$, respectively, and no other serious complication was recognized. Patients with performance status of 2 or worse or

creatinine clearance of <60 ml/min. and those who had grade 4 bone marrow toxicity from the treatment for 3 days or more had a 25% dose reduction of all four agents. In patients having two dose-reduction criteria, therefore, the dosage was reduced to 60% of the full dose.

Response was evaluated using physical examination, radiography, CT scan, and/or ultrasonography at least every two cycles of treatment. Response criteria were defined as follows: complete response (CR) as complete disappearance of all evidence of tumor by the above-mentioned diagnostic tests for more than 1 month; partial response (PR) as greater than 50% regression of the summed products of the longest perpendicular diameters of all measured lesions by diagnostic tests for more than 1 month; no change as less than 50% decrease or less than 25% increase in tumor size for more than 1 month; and progressive disease as any 25% or more increase in tumor size or the appearance of new lesions. The response of osteolytic metastasis was defined as PR when complete or nearly complete recalcification was found (Fig. 1). Otherwise, the response was defined as incomplete. Patients who did not show any response were taken out of the study. Blood count, blood chemistry, creatinine clearance measurement and physical examination were regularly performed and toxicity was graded according to the WHO criteria.

Patients who responded well to the chemotherapy but had apparently resectable lesions were recommended to undergo surgical resection following the chemotherapy. In addition, patients who had viable cancer cells in resected specimens were also recommended to receive additional chemotherapy of two or three cycles. All of the 29 patients were evaluated for both response and toxicity.

Survival of patients was estimated by the Kaplan-Meier method [9] and the log rank test was used to analyze differences in the survival curves.

Results

A total of 29 patients with metastatic lesion(s) from carcinoma of the urinary bladder or upper urinary tracts were enrolled in this study. They were consecutive patients treated from February 1994 to August 1998 at our clinics and had measurable lesions on CT scan, ultrasonography and/or plain radiography. Patient characteristics are shown in Table 1. A majority of patients were male and their ages ranged from 33 to 79 years. Performance status was 0–1 in 17 patients, and 2–3 in 12. Nearly half the patients had anemia and/or renal dysfunction as reflected by a median pretreatment blood hemoglobin level of 11.3 g/dl and a median creatinine clearance of 66 ml/min. Ten patients had a history of prior treatment including seven who had been treated with cisplatin-containing chemotherapy. Primary disease was bladder cancer in 15, renal pelvic or ureteral cancer in 10 and both bladder and upper urinary tract cancers in 4. The histologic diagnosis of the primary lesion was transitional cell carcinoma (TCC) in 23 and TCC plus other pathology (adenocarcinoma or squamous carcinoma or both) in 6. Of the 29 patients, 14 had only lymph node metastasis, while 15 had visceral metastasis with or without lymphatic spread. Evaluable lesions were located in lymph nodes, primary organs, lung, bone, liver and other locations in descending order (Table 2). Analgesic medication was needed by 15 patients for grade 2 or more pain due to metastatic disease.

The number of chemotherapy cycles given ranged from one to eight with a median of four. The mean value of dose intensity of the chemotherapy was 87% in the first cycle, and 81%, 77% and 74% in the subsequent ones. Response was achieved in 17 patients (58.6%). The response rate was not associated with any particular patient profile including metastatic site as shown in Tables 1 and 2. Osseous metastases also responded well in four of six patients as evidenced by recalcification of lytic lesions (Fig. 1), resulting in marked pain relief, but all of these patients died of disease progression 8 to 13 months after initiation of the chemotherapy. Of 15 patients who had pain of grade 2 or more, 9 (60%) had complete resolution. Ten patients who had achieved a nearly complete or a partial response underwent surgical removal of residual disease following two to five cycles of chemotherapy (median three). Although all of them had viable cancer cells in resected specimens, postoperative chemotherapy was given to only three patients. The number of cycles was two in one patient and three in two. In the other seven patients, adjuvant chemotherapy

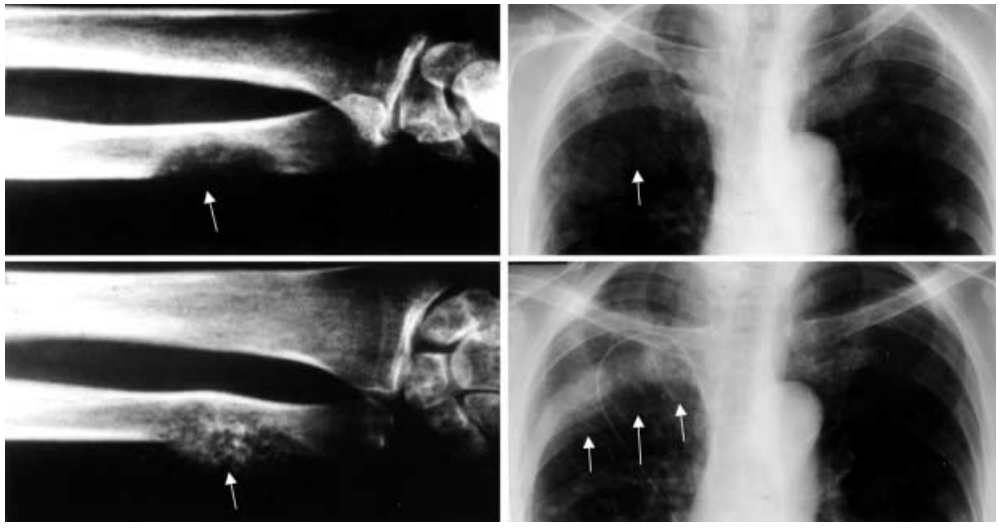

Fig. 1 Left: Nearly complete recalcification of osteolytic metastasis in the ulna of a 72-year-old female patient with ureteral cancer. Right: The right fifth rib of a 67-year-old female with bladder and ureteral cancer

Table 1 Relationship of patient profile to the rate of response (CR + PR) to IFEP chemotherapy and survival time of the patients

	Median (range)	Number of patients	Response rate	Survival time (days)		
				Median	Mean	*P*-value
Total no. of patients		29	58.6	422.0	605.8	–
Gender						
Male		21	52.4	421.0	606.9	0.4944
Female		8	75.0	305.0	435.5	
Age (years)	62 (33–79)					
< 65		14	57.1	448.0	797.1	0.0519
≥65		15	60.0	345.0	367.9	
Performance status						
0–1		17	52.9	453.0	835.2	0.0003
2–3		12	66.7	250.5	290.1	
Hemoglobin (g/dl)	11.3 (6.0–14.7)					
< 11.3		14	71.4	342.0	410.2	0.3153
≥11.3		15	46.7	409.0	690.5	
Creatinine clearance (ml/min)	66 (32–93)					
< 66		11	45.5	378.0	389.7	0.237
≥66		12	58.3	410.0	804.3	
Prior treatment						
No		19	57.9	421.0	662.4	0.3708
Yes		10	60	373.5	409.3	
Primary tumor						
Bladder		15	60.0	425.0	670.3	0.4526
Upper urinary tract + bladder		14	57.1	361.5	447.6	
Pathology						
TCC		23	65.2	408.0	460.5	0.3627
TCC + other		6	33.3	461.0	842.1	
Stage						
N2–3		14	64.3	464.0	716.9	0.0277
M1		15	53.3	312.0	389.1	
Pain						
No		14	64.3	417.0	686.4	0.575
Yes		15	53.3	369.0	442.5	
Response to IFEP						
PR		17	–	409.0	622.7	0.697
NC-PD		12	–	393.0	453.0	
Initial dosage of IFEP						
100%		15	46.7	453.0	851.4	0.0206
≤ 75%		14	71.4	342.0	361.1	

Table 2 Response rate according to site of disease and the presence of pain

Site	No. evaluable	CR	PR	CR + PR (%)
Lymph node	20	2	11	65
Pulmonary	9	0	5	56
Osseous	6	0	4	67
Hepatic	4	1	1	50
Primary	17	2	8	59
Other[a]	4	1	3	100
Pain	15	9	4	87

[a]Skin, penile cavernosum, gluteal muscle and mesentery

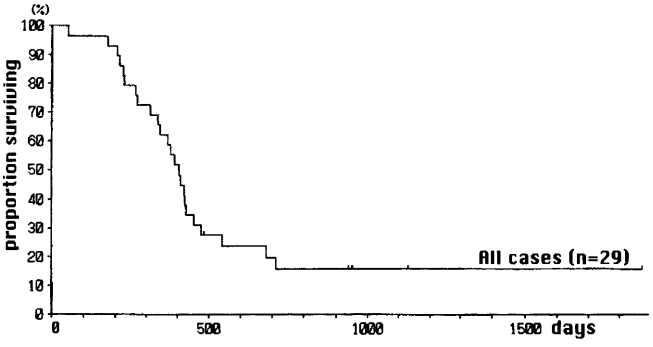

Fig. 2 Kaplan-Meier survival curve for all the patients

was not given because of patient refusal (three patients) or physician's discretion (very good or incomplete pathological response each in two patients).

The overall survival curve of the 29 patients is shown in Fig. 2. None of the patients was lost to follow-up. Although 62% of the patients survived 1 year, only 16% survived 3 years. The median and mean survival times of all the patients were 14 and 20 months, respectively. Of the ten patients who underwent salvage surgery, four (three with lymph node metastases alone and one with pulmonary metastasis) were alive with no evidence of disease 15 to 61 months after the onset of treatment.

One patient with metastases to the penile cavernosum and pelvic lymph nodes was alive with lymph node recurrence 37 months after treatment and five others died of the disease. Among pretreatment patient characteristics, good performance status (0–1) and initially receiving full-dose chemotherapy had a significantly favorable impact on survival, but visceral metastasis was an unfavorable prognostic feature compared to lymph node metastasis alone as shown in Fig. 3. The 5-year survival rate was 28% in 17 patients with good performance status, 32% in 15 who had received full-dose chemotherapy and 23% in 11 patients with lymph node metastases alone. No other clinicopathological profiles including response to the chemotherapy significantly affected patient survival (Table 1).

Bone marrow toxicity was significant (Table 3). Leukocytopenia and thrombocytopenia of grade 3 and 4 were found in 90% and 45% of the patients, respectively. Administration of granulocyte colony-stimulating factor and platelet transfusion was given to 26 patients (90%) and 6 patients (21%), respectively. Granulocytopenic fever occurred in nine patients (31%), one of whom died of septicemia after the eighth cycle treatment. Other toxicities were mild to moderate, except grade 3 delirium probably due to ifosfamide in one patient and grade 3 diarrhea in two patients. Renal dysfunction was not associated with the severity of toxicities probably because the dosage was reduced according to decrease in creatinine clearance. Of note, there was no episode of serious stomatitis.

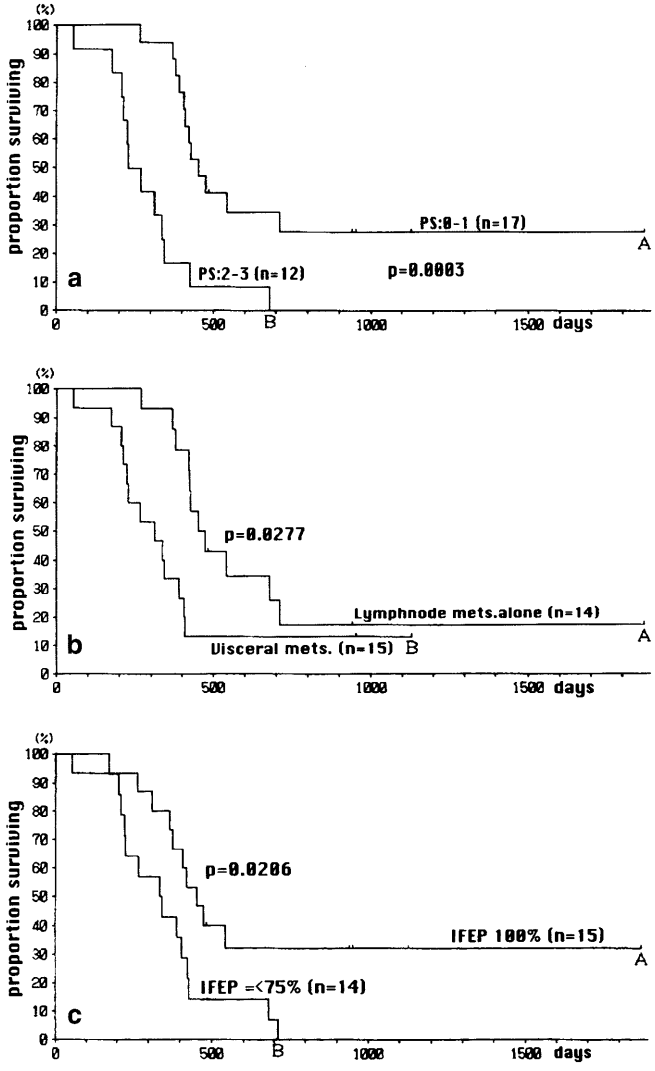

Fig. 3A–C Survival curves according to the patients' performance status (**A**), metastatic site (only lymph node vs visceral metastasis) (**B**) and the initial dosage of the chemotherapy (**C**)

Discussion

In the treatment of metastatic urothelial cancer, cisplatin-containing chemotherapy still appears to be a standard regimen. Although the activities of new drugs such as gallium nitrate, taxanes and gemcitabine have been investigated [2, 11, 16, 17], cisplatin, methotrexate and vinblastine with or without doxorubicin (CMV [7] and M-VAC [1, 8, 14, 15]) appear to be widely accepted. Although the immediate response rates achieved with these regimens are relatively good with a range of 40% to 69%, long-term patient survival is dismal with a median survival time of 8 to 13 months. In a prospective randomized trial comparing the M-VAC regimen with cisplatin alone [12], survival at 6 years was only 3.7% in 133 patients randomized to M-VAC. In addition, the dose schedule of

Table 3 Toxicity of IFEP chemotherapy

Toxicity	Grade of toxicity			
	0	1–2	3	4
Leukocytopenia	0	3 (10.3%)	15 (51.7%)	11 (37.9%)
Thrombocytopenia	2 (6.9%)	14 (48.3%)	9 (31.0%)	4 (13.8%)
Anemia	2 (6.9%)	12 (41.4%)	14 (48.3%)	–
Renal dysfunction	20 (69.0%)	9 (31.0%)	0	0
Hepatic dysfunction	24 (82.8%)	5 (17.2%)	0	0
Nausea/vomiting	7 (24.1%)	17 (58.6%)	5 (17.2%)	–
Diarrhea	24 (82.8%)	3 (10.3%)	2 (6.9%)	0
Mucositis	27 (93.1%)	2 (6.9%)	0	0
Alopecia	0	14 (48.3%)	15 (51.7%)	–
Delirium	28 (96.6%)	0	1 (3.4%)	–
Granulocytopenic fever	20 (69.0%)	9 (31.0%)	0	–

these regimens, especially administration of methotrexate and vinblastine on days 15 and 22, is complicated and toxicity including bone marrow suppression, nausea and vomiting, and stomatitis is considerable. Therefore, we designed a new combination regimen.

Previously, we studied a three-drug regimen consisting of ifosfamide, 5-FU and cisplatin (IFP), and confirmed its safety and moderate activity in the treatment of both of prostatic [10] and bladder cancer (unpublished data). In the current study for urothelial cancer, we added etoposide to the IFP along with dose escalation of 5-FU from 1250 to 2250 mg/m^2 per cycle. 5-FU and ifosfamide, as well as cisplatin, are known to be active as single agents in the treatment of urothelial cancer [3, 11, 19]. Although the effectiveness of etoposide in urothelial cancer remains unsettled [5, 18], this drug as well as ifosfamide and 5-FU has been reported to show synergistic activity when given together with cisplatin [13]. Indeed, with a two-drug regimen with etoposide and cisplatin, a response rate of 41% has been achieved in the treatment of advanced TCC [6]. Thus, we launched a study of the four-drug combination of ifosfamide, 5-FU, etoposide and cisplatin.

Although the overall response rate of 59% achieved with the IFEP regimen may not be superior to those with the CMV and M-VAC regimens [1, 7, 8, 14, 15], some benefits of the IFEP regimen can be mentioned. For example, the dose schedule of 3-day treatment every 3 weeks is simple, and, although the number of patients studied was small, the response rate of 67% in bone metastasis seems better than in previous studies [8]. Further, in patients with good performance status or lymph node metastasis alone, patient survival may be improved by full-dose chemotherapy followed by removal of residual disease as indicated in the study by Sternberg et al. [14]. All of four patients in the current study who were alive with no evidence of disease at the time of this report underwent salvage surgery. Although the usefulness of additional adjuvant chemotherapy following salvage surgery remains unclear, the presence of viable cancer cells in resected specimens may indicate the necessity for adjuvant chemotherapy.

The toxicity of the IFEP regimen is considerable and bone marrow toxicity may be more significant than that seen in M-VAC series [1, 8, 14, 15]. However, it can be stressed that constitutional toxicity appeared to be mild to moderate in the current study, and in particular mucositis causing anorexia and even delay of drug administration rarely occurred.

In conclusion, the IFEP regimen appears to be active in the treatment of metastatic urothelial cancers, and, particularly for patients with good performance status and/or lymph node metastasis alone, full-dose chemotherapy followed by salvage surgery may be curative. Although bone marrow toxicities were significant, the treatment should be well tolerated by the majority of patients. Further study may be warranted.

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