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Combination chemotherapy including Adriamycin for advanced transitional cell carcinoma of the urinary tract

Toshihiko Kotake[1], Michiyuki Usami[1], Tsuneharu Miki[1], Masao Kuroda[1], Koji Obata[2], Masao Osafune[3], Hideki Fujioka[3], and Yutaka Takasugi[4]

[1] Department of Urology, The Center for Adult Diseases, Osaka, 1–3–3 Nakamichi, Higashinariku, Osaka 537, Japan
[2] Department of Urology, Nagoya Second Red-Cross Hospital, 2–9 Myokencho, Showaku, Nagoya 466, Japan
[3] Department of Urology, Osaka University Hospital, 1–1–50 Fukushima, Fukushimaku, Osaka 553, Japan
[4] Department of Urology, Osaka Prefectural Hospital, 3–1–56 Mandaihigashi, Sumiyishiku, Osaka 558, Japan

Summary. *Thirty-three patients with advanced transitional cell carcinoma of the urinary tract (23 bladder cases, 8 ureter cases, and 2 renal pelvis cases) were treated by three-drug combination chemotherapy using two protocols (protocol I: Adriamycin 50 mg/m², cyclophosphamide 500 mg/m², and 5-fluorouracil 500 mg/m², protocol II: Adriamycin 50 mg/m², cyclophosphamide 500 mg/m², and cis-platinum 50 mg/m²). Protocol I induced responses in three of 19 patients (16%), (1 complete response, 2 partial responses), and protocol II (1 complete response, 4 partial responses) in five of 14 patients (36%). The overall response rate was 24%. The duration of response was relatively short (median duration 5.1 months). The combination therapy was relatively well tolerated except in three patients, including two mortalities. In our study, three-drug combination chemotherapy with Adriamycin, especially that including cis-platinum, was effective against transitional cell carcinoma of the urinary tract, but the results were not completely satisfactory.*

Introduction

Patients with advanced carcinoma of the urinary tract relapsing or persisting after conventional forms of therapy, including surgery and/or radiotherapy, have a poor prognosis and when distant metastases develop seldom survive for more than a few months. In the majority of these patients surgery or radiotherapy is of no value, and their management has become an important problem. Systemic chemotherapy has been thought to be the most useful treatment for these patients. Recently, several chemotherapeutic agents have been studied singly or in combinations. While chemotherapy for advanced urothelial cancer in general has been discouraging, Adriamycin, cyclophosphamide, and 5-fluorouracil have been extensively evaluated [3]. Reports recently summarized by deKernion indicate that Adriamycin, cyclophosphamide, and 5-fluorouracil, respectively, induced responses in 23%, 41%, and 39% of cases of advanced transitional cell carcinoma [7]. The use of the two-drug combination of Adramycin and cyclophosphamide yielded responses in 17%–50% [12, 27] and the combination of Adriamycin with 5-fluorouracil, in 35% [2, 5]. More recently, Yagoda and co-workers initiated clinical trials with *cis*-platinum (DDP) for advanced urothelial cancer, and reported a response rate superior to any single agent examined previously [26]. Studies of these drugs led us to examine their effectiveness when used in combination.

In the present study, three-drug combination chemotherapy based on two protocols using Adriamycin and cyclophosphamide with 5-fluorouracil or DDP was administered to 33 patients with advanced transitional cell carcinoma of the urinary tract. The study was conducted jointly by four clinics.

Materials and methods

The study included 33 patients with advanced transitional cell carcinoma, who were treated with a three-drug combination chemotherapy including Adriamycin. Their pretreatment data are shown in Table 1. The male : female ratio was 29 : 4, and the mean age was 59 years (33–74). Of the tumors, 23 originated from the bladder, eight from the ureter, and two from the renal pelvis. Prior treatment for the primary tumors was ascertained in the 23 patients with bladder carcinoma: 18 patients had been treated by total cystectomy and urinary diversion, two patients by partial cystectomy, and one patient by transurethral resection; and two patients had undergone transurethral biopsy and ureterocutaneostomy without any other surgical treatment. All 10 patients with ureteral and renal pelvic tumors had undergone total nephroureterectomy. All patients had a previous diagnosis of transitional cell carcinoma of the urinary tract confirmed histologically. The histopathological grading of the tumors according to the UICC classification was G1, G2, and G3, in three, eight, and 22 cases, respectively [20]. The predominant and measurable sites of disease involvement included regional or peripheral lymph nodes (iliac, para-aortic, and supraclavicular) in 20 patients, lung in 13 patients, pelvic or retroperitoneal local extension in 11 patients, and bone, liver, skin, and invasive primary bladder tumors in five, two, one, and two patients, respectively (Table 2).

All patients were evaluated initially and at weekly intervals by the following studies: physical examination, body weight and height, complete blood and platelet count, routine chemical profile, urinalysis, 24-h urine creatinine clearance, electrocardiogram, and chest X-ray. The extent and nature of any residual tumor in the bladder was determined by cystoscopy, transurethral ultrasonogram, and transurethral biopsy. The presence and size of measurable metastases were determined by radiology, liver, scan, bone scan, computed

Reprint requests should be addressed to T. Kotake

Table 1. Patients' characteristics

	No. of patients		
	Total	Protocol I	Protocol II
Total no. of patients	33	19	14
Male	29	16	13
Female	4	3	1
Average age	59	63	53
Range	32–74	48–71	32–74
Sites of primary tumor			
Bladder	23	14	9
Ureter	8	5	3
Renal pelvis	2	0	2
Grading of differentiation			
G 1	1	1	0
G 2	10	4	6
G 3	22	14	8
Prior treatment for primary tumor			
Total cystectomy	18	10	8
Partial cystectomy	2	1	1
TUR bt	1	1	0
Nil (ureterocutaneostomy)	2	2	0
Total nephroureterectomy	10	5	5
Sites measurable of disease			
Lymph nodes	20	14	6
Lung	13	6	7
Local extention	11	7	4
Bone	5	3	2
Liver	2	1	1
Bladder tumor	2	2	0
Skin	1	0	1

Table 2. Results of combination chemotherapy including Adriamycin

Treatment		Response			Total
		CR + PR	MR + SD	PD	
Protocol I:	No. of patients (%)	1 + 2 (16)	4 + 7 (58)	5 (26)	19
Protocol II:	No. of patients (%)	1 + 4 (36)	2 + 2 (28)	5 (36)	14
Totals	No. of patients (%)	2 + 6 (24)	6 + 9 (46)	10 (30)	33

tomogram, and ultrasonogram. The pretreatment performance status was ambulatory (over 50% according to the Karnofsky performance scale) in 30 patients and bedridden (under 50%) in three patients. None of these patients had heart disease or hematological abnormality.

The combination chemotherapy was performed according to two protocols. Protocol I consisted of Adriamycin 50 mg/m^2 IV on day 1, cyclophosphamide 500 mg/m^2 IV on day 1, and 5-fluorouracil 500 mg/m^2 IV on days 2–6. In protocol II, Adriamycin 50 mg/m^2 was given IV on day 1 in combination with cyclophosphamide 500 mg/m^2 IV on day 1 and with DDP 50 mg/m^2 IV on day 2. For the 5 h preceding the administration of DDP patients were hydrated by infusion of 1,000 ml 5% dextrose in normal saline IV followed by infusion of 12.5 g mannitol and 20 mg furosemide IV. Then DDP 50 mg/m^2 was mixed in 500 ml 5% dextrose and given IV over 4 h, followed by 1,500 ml fluids and electrolytes over 5 h. Antiemetics were given regularly 14 h after DDP. DDP (as NK-801) was supplied by the Pharmaceutical Division of Nippon Kayaku Co., Tokyo. These 7-day courses were repeated every 21 days. All patients received at least two courses of the combination chemotherapy. Response was evaluated as follows: complete remission (CR): complete disappearance of all recognizable disease; partial remission (PR): 50%–99% decrease in the sum of the products of two diameters of all lesions; minor response (MR): 25%–49% regression in area of a measurable mass; stable disease (SD): less than 25% decrease or increase in initial tumor size; progressive disease (PD): greater than 25% increase of any lesions. The three categories of MR, SD, and PD were not included in the overall objective response rate. The assessment was collectively made on the basis of all examinations including X-ray examination. Duration of response and survival were calculated from the onset of treatment.

Table 3. Response according to sites of metastases

Site	No. of patients	Response		
		CR + PR	MR + SD	PD
		No. of patients (%)	No. of patients (%)	No. of patients (%)
Lymph nodes	20	1 + 5 (30)	5 + 6 (55)	3 (15)
Lung	13	2 + 1 (23)	2 + 2 (31)	6 (46)
Local extension	11	1 (9)	1 + 3 (36)	6 (55)
Bone	5		2 + 2 (80)	1 (20)
Liver	2		1 (50)	1 (50)
Skin	1			1 (100)
Bladder	2		1 (50)	1 (50)

Results

Thirty-three patients were entered on the study and all patients were evaluated in terms of response and toxicity. Protocol I was administered to 19 patients and protocol II, to 14 patients. The two groups were similar in patients' characteristics. The mean number of courses given was 3.5, with a range of 2–9. Of the 33 patients, 13 patients continued with treatment for more than 3 months, and 20 patients for less. The treatment results are summarized in Table 2. Of 19 patients receiving protocol I, 16% showed an objective response (1 CR and 2 PR), and 58% remained stable (4 MR and 7 SD). In five patients the disease progressed. Among the 14 patients treated according to protocol II, one complete and four partial remissions were observed, and there were two MR, seven SD, and five PD. The response rate of 36% with protocol II was better than that obtained with protocol I. The overall objective response rate in the study was 24%. The eight responses were seen in five (22%) of 23 patients with transitional cell carcinoma from the bladder, in two (25%) of eight patients with carcinoma of the ureter, and in one (50%) of two patients with metastasis from the renal pelvis. The effects of treatment on individual

Table 4. Duration of response to combination chemotherapy including Adriamycin

Treatment	Total	Response		
		CR + PR	MR + SD	PD
Protocol I:				
No. of patients	19	3	11	5
Median duration (months)		4.7	5.0	–
Range		2–8	1–21	
Protocol II:				
No. of patients	14	5	4	5
Median duration (months)		5.4	4.3	–
Range		4–9	2–9	
Total:				
No. of patients	33	8	15	10
Median duration (months)		5.1	4.8	–
Range		2–9	1–21	

measurable lesions are shown in Table 3. Responses in lymph nodes were observed in six patients (1 CR and 5 PR), in lung in three (2 CR and 1 PR), and in the local tumor mass in one (PR). There were no objective responses in primary bladder tumors, bone metastases, liver metastases, or skin metastases.

The durations of response are shown in Table 4. The median duration of response was 5.1 months, with a range of 2–9 months in eight patients in whom objective response was achieved, and 4.8 months with a range of 1–21 months in 15 patients in whom disease remained stable. Of the 33 patients, 10 are surviving, with the longest survival being 24 months; this patient achieved partial remission after four courses according to protocol I. The shortest survival was 2 months, and eight patients died less than 3 months after initiation of the treatment. Five patients were followed for more than 12 months, and the median survival was 6.7 months (Table 5). Patients with measurable response survived longer: the median survival in patients in whom objective response was achieved was 11 months, as against 7.1 months and 2.6 months for patients remaining stable and those showing progression of disease, respectively.

Toxicities of combination chemotherapy, including the two mortality cases, are listed in Table 6. The most common toxicities were gastrointestinal toxicity, alopecia, and bone marrow suppression. Gastrointestinal toxicity, including anorexia, nausea, and vomiting occurred in almost all patients but was controlled with antiemetic drugs; in no patient did it result in discontinuation of treatment. Vomiting and severe nausea were observed more often in patients treated with protocol II than with protocol I. In three patients abnormal changes in liver function tests were noted. Only one patient treated according to protocol II, which included DDP, showed a moderate decrease of the renal function. Cardiotoxicity occurred in two patients during therapy; in one of these sudden death occurred after two courses of protocol I, at a cumulative dose of 100 mg/m^2 without changes in ECG or physical examinations from before treatment, while the other patient developed severe tachycardia without any change in ECG after four courses of protocol II at a cumulative dose of 200 mg/m^2, completely recovering after 2 weeks with no ECG change but receiving no further therapy. Leukopenia developed in 73% of patients, thrombocytopenia in 27%, and anemia in 45%. Myelosuppression usually occurred between day 10 and day 15

Table 5. Duration of survival attained with combination chemotherapy including Adriamycin

Treatment	Total	Response		
		CR + PR	MR + SD	PD
Protocol I:				
No. of patients	19	3	11	5
Median duration (months)		13.0	7.5	2.2
Range		4–24	3–21	2–3
Protocol II:				
No. of patients	14	5	4	5
Median duration (months)		9.8	6.0	3.6
Range		4–13	4–9	2–10
Total:				
No. of patients	33	8	15	10
Median duration (months)		11.0	7.1	2.9
Range		4–24	3–21	2–10
No. of surviving patients (%)	10 (30)	5 (63)	5 (36)	0 (0)

Table 6. Toxicities of combination chemotherapy including Adriamycin

Toxicities	Protocol I		Protocol II		Total	
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Lassitude/ anorexia	15	(79)	14	(100)	29	(89)
Nausea/ vomiting	4	(21)	12	(86)	16	(49)
Hepatic	2	(10)	1	(7)	3	(9)
Alopecia	16	(84)	12	(86)	28	(85)
Fever	3	(16)	–	(–)	3	(9)
Pulmonary	–	(–)	1	(7)	1	(3)
Renal	–	(–)	1	(7)	1	(3)
Neurologic	–	(–)	1	(7)	1	(3)
Cardiovascular	1[a]	(5)	1[b]	(7)	2	(6)
Leukopenia	14	(74)	10	(71)	24	(73)
Thrombocytopenia $< 10^5$	5	(26)	4	(29)	9	(27)
Anemia	8	(42)	7	(50)	15	(45)

[a] Cardiac death
[b] Severe tachycardia: recovered after 2 weeks

during the course, but the recovery of blood cells was extremely rapid and was completed by day 21. Some patients required blood transfusion and administration of antibiotics. One patient, who achieved CR with four courses of protocol I, had prolonged myelosuppression and finally died of irreversible anemia.

Discussion

Although transitional cell carcinoma of the urinary tract, i.e., bladder, ureter, and renal pelvis, is considered to be a chemotherapeutically responsive tumor, the present role of chemotherapy in patients with these tumors is unclear. Treatment for advanced disease must be directed at eradication of all lesions, which can only be achieved presently by

surgery or systemic chemotherapy. There are a number of studies dealing with systemic chemotherapy of advanced urothelial cancer, but in most studies patients' characteristics, criteria of response, and treatment methods have not been homogenous, which makes it difficult to compare the results obtained in the various series. Of several cytotoxic drugs, Adriamycin, cyclophosphamide, and 5-fluorouracil have been extensively evaluated [3, 7, 9, 13], and the most active drug seems to DDP in the treatment of urothelial cancer [9, 17, 25]. Generally, combination chemotherapy is more effective than single-agent therapy. In our study, therefore, we decided to use a combination of Adriamycin, cyclophosphamide, and 5-fluorouracil or DDP.

Initial reports on the use of Adriamycin as a single agent seemed encouraging, with objective responses of 35%–57%, but subsequent studies revealed remissions in only 12%–25% [23]. The use of the two-drug combination of Adriamycin and cyclophosphamide has been reported to induce remissions in 17%–50% of cases [12, 27], and a combination of Adriamycin and 5-fluorouracil has yielded responses in 30%–40% [8, 16, 21]. The 16% response rate to the three-drug combination of Adriamycin, cyclophosphamide, and 5-fluorouracil in our study was disappointing. Smalley et al. reported a response rate of only 15% with the same three-drug combination in 21 patients with advanced bladder cancer [15]. It is discouraging that the three-drug combination in protocol I has not given better results than these drugs as a single agent. However, it is of interest that of 19 patients treated with protocol I, in 11 (58%) disease remained stable (4 MR, 7 SD) for 5 months, with a longer duration of survival than in patients with progressive disease. On the other hand, the 36% response rate of protocol II, with the combination of Adriamycin, cyclophosphamide and DDP, is remarkably similar to that reported by other authors with the same three-drug combination: 33% by Troner [19], 42% by Samueles [14], and 50% by Yagoda [24]. Williams et al. have also reported a similar response rate (46.2%) with a combination of Adriamycin, DDP, and 5-fluorouracil [22]. Furthermore, a higher response rate with Adriamycin, cyclophosphamide, and DDP has been reported by Sternberg et al. (83%) in 12 patients with advanced urothelial cancer [18], and by Kedia et al. (82%) in 23 patients [10]. Thus, in our study protocol II a DDP-containing regimen, appears to have some activity in advanced urothelial cancer, and it seems to be superior to protocol I. However, the responses with both protocols have been of short duration, and responding patients survived for only slightly longer than non-responders. No significant difference between the two treatment approaches was demonstrable in duration of either response or survival. It is not yet known whether such chemotherapeutic modalities will prolong survival. At present, combination chemotherapy with Adriamycin, DDP, and cyclophosphamide or 5-fluorouracil has given the highest response rate of any protocol in advanced, metastatic transitional cell carcinoma of the urinary tract [25]. However, these data still do not indicate any additive or synergistic benefit with Adriamycin, cyclophosphamide, or 5-fluorourcil or combination of these agents in DDP-containing regimens. A reliable comparison of these regimens in treatment of advanced urothelial cancer requires a greater number of patients, preferably in a controlled trial.

Combination chemotherapy was quite well tolerated except in three patients. Toxicity levels in our study, associated with two mortalities, are listed in Table 6. Most toxicities were controlled with medicamentation. Specifically, the cardiotoxicity and clinical importance of Adriamycin are well known [1, 11]. In our study, cardiotoxicity occurred in two patients; in one of them 'sudden death' occurred after two courses of protocol I, while the other developed severe tachycardia after four courses of protocol II but completely recovered after 2 weeks. There are a number of studies on detection of early cardiotoxicity in patients [6]. We are interested in the use of co-enzyme Q_{10} for the prevention of cardiotoxicity and alopecia [4]. Hematological toxicity occurred in most patients, and one patient died of irreversible severe anemia. Such patients should be given prompt treatment, including blood transfusion and administration of adequate antibiotics. Our data suggest that the dosage employed in the present study conducted in Japanese patients produced a considerable incidence of toxicity, which requires further investigations.

Although it is difficult to draw conclusions from this small non-randomized study, the three-drug combination chemotherapeutic modality including Adriamycin and DDP appears to be the most effective for advanced urothelial cancer. We are therefore currently conducting larger-scale clinical trials with these regimens in controlled prospective studies.

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