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THERAPEUTIC EXPERIENCE OF ADVANCED UROTHELIAL TRACT TUMORS

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Twenty-three patients with locally advanced and/or metastatic urothelial tumors were treated by surgery, chemotherapy or radiation. Radical operation with or without radiation resulted in tumor free conditions in 8 patients. Fifteen patients who had a few dimensionally estimable disease parameters, underwent chemotherapy. Objective responses were obtained in 6 of the 15 patients (1 CR and 5 PR). The objective response of low grade or low stage tumors or cases with high Karnofsky performance ratings was moderate. Combination chemotherapy with cisplatin (CDDP), doxorubicin (ADM) and cyclophosphamide or a CDDP-containing combination appeared to be beneficial for patients with advanced urothelial tract tumors with palliative purpose.

Key words: Advanced bladder tumor, Transitional cell carcinoma, Chemotherapy, Cisplatinum, Doxorubicin

INTRODUCTION

Transitional cell carcinoma of the urinary tract remains the most common malignancy and, despite the success of surgery, chemotherapy or radiotherapy at the initial stage of cancer, the mortality of advanced bladder cancer is high[1~3]. For patients with recurrent or metastatic cancer, chemotherapy has become a valuable method of treatment. Combinations of some antitumor agents have provided excellent results. Unfortunately, however, the duration of remission has been short, and treatment has occasionally failed to produce objective responses due to excessive toxicity. In addition, transitional cell carcinoma is well known to occur multiply and it may involve any portion of the urothelium[4]. Such complexity may explain why relatively few pathological or clinical reports have been made on the treatment of advanced uroepithelium. This paper is primarily concerned with chemotherapy in patients with advanced transitional cell carcinomas of uroepithelium.

MATERIALS AND METHODS

Twenty-three patients, 16 men and 7 women, with advanced and/or metastatic transitional cell carcinoma of the urinary tract were the main subjects of the study. Table 1 shows the clinical data and relevant tumor characteristics for these patients. Red and white blood cell counts, hemoglobin, thrombocyte count, LDH, CRP, blood urea nitrogen (BUN), serum creatinine (Cr), and erythrocyte sedimentation rate (ESR) were determined at the beginning and at various times throughout the treatment period. Other pretreatment evaluations included bone scintigram, chest X-rays, excretory urogram, cystogram, cystoscopy, pelvic arteriogram, lymphangiogram, bimanual palpation under lumbar anesthesia and echogram. Biopsies on selected sites as well as suspicious regions of the bladder wall were done prior to treatment and during the follow-up period. The carcinoma could be graded according to cellular pattern and nuclear features of the cytological criteria of Bergkvist and associates[5]. Tumors were staged according to

Table 1. Clinical and pathological data for patients with advanced urothelial tract tumors

Patient characteristics

Total No. of patients : 23 (100)
Male : 16 (89.6)
Female : 7 (30.4)

Mean Age : ±S.E. : 70±2
Range : 41−83

Sites of primary tumor : 23 (100)
Bladder : 19 (82.6)
Ureter : 3 (13.0)
Renal pelvs : 1 (4.3)

Therapy for primary tumor :

Total cystectomy	7 (14.9)
Ureterocutaneostomy	8 (17.0)
Ileal conduit	2 (4.3)
TUR-Bt	7 (14.9)
Nephroureterectomy	4 (8.5)
Partial cystectomy	5 (10.6)
Hyperthermia	3 (6.4)
Nephrostomy	1 (2.1)
Lymphnode resection	2 (4.3)
Radiation	8 (17.0)
Total	47 (100)

Tumor characteristics

Histological findings :
TCC : 22 (95.7)
Squamous cell carcinoma : 1 (4.3)

Grade :
II : 3 (13.0)
III : 20 (87.0)

TNM classification :

(T)		(N)		(M)	
Tis	1 (4.3)	N_0	13 (56.5)	M_0	15 (65.2)
T_2	2 (8.7)	N_1	1 (4.3)	M_1	8 (34.8)
T_{3a}	6 (26.1)	N_2	3 (13.0)		
T_{3b}	7 (30.4)	N_3	1 (4.3)		
T_{4a}	4 (17.4)	N_4	5 (21.7)		
T_{4b}	3 (13.0)				

( ) : %

the TNM classification[6]. All ambiguous lesions were appraised and classified at observed times as measurable valuables. Peripheral lesions were measured by the same physicians employing the longest and perpendicular diameters. Fifteen patients with advanced and/or metastatic urothelium tumors were selected as candidates of chemotherapy. The mean given doses were not always close to the calculated doses for each drug. Typical chemotherapies performed in this study were as follows: intravenous infusion of 1,200 mg/day of 5-fluorouracil (5-FU) for 30～34 consecutive days; hyperthermia of bladder cavity using 120 mg of bleomycin daily or 100 mg of pepleomycin daily for consecutive 10 days; intravenous administration of 30～50 mg/m^2 of cisplatin (CDDP), 30～50 mg/m^2 of doxorubicin (ADM) in combination with 200～500 mg/m^2 of cyclophosphamide (CTX) for 2～3 cures; intravenous injection of 4 mg of mitomycin C (MMC) in addition to 10 mg of ADM once a week for 8 weeks; 30～50 mg/m^2 of CDDP for 2～3 cures in addition to intravenous injection of 1,200 mg/day of 5-FU for 30 days. Responsive criteria was classified as 1) complete remission (CR)-complete disappearance of tumor and complete resolution of all tumor-related symptoms, 2) partial response (PR)-≧50% decrease in tumor size or sum products of the 2 diameters of all measurable lesions, 3) stable disease (SD)-25%～49% shrinkage in initial tumor size or tumor related mass, for over one month or a partial remission shorter than one month, 4) progressive disease (PD)->25% increase in tumor size when measured from the maximum response. The Karnofsky performance scale was used for the evaluation of the subjective changes.

RESULTS

Our data suggest that total cystectomy or total nephroureterectomy with or without radiation appears to be one of the more effective treatments in patients with ad-

Table 2. Response according to various treatments

Treatment	No. of Responder (14)	No. of Non-responders (9)
* Radical operation+Chemotherapy	3	1
* Radical operation+Chemotherapy+Radiation	5	1
TUR-Bt+Chemotherapy	5	2
Partial cystectomy+Chemotherapy	1	1
Others	0	4

* Radical operation : Total cystectomy in bladder tumor or nephroureterectomy +Partial cystectomy in ureter or renal pelvic tumor.

( ) : Number of patients.

Table 3. Age, sex, performance status and laboratory data of patients before treatment

Variables		Responders (14)	Non-Responders (9)
Mean age±S.E.		69±3	72±2
Sex(male : female)		10 : 4	6 : 3
Performance status on Karnofsky's scale	60≦	11	4*
	60>	3	5
White blood cell count(mm^3)		6821±1054	7764±1512
Red blood cell count($\times 10^4/mm^3$)		377±15	384±24
Hb(g/dl)		12.3±0.5	12.0±0.7
Thrombocyte($\times 10^4/mm^3$)		254±17	272±25
LDH(U/l)		138±7	173±21
CRP	2(+)≦	3	1
	2(+)>	11	7
BUN(mg/dl)		22±5	23±5
Creatinine(mg/dl)		1.7±0.6	1.3±0.3
ESR(mm)	30min.	13±3	30±10
	60min.	33±9	61±15
	120min.	62±12	97±16

* $p<0.05$ compared to responders (binomial distribution)

( ) : Number of patients.

vanced uroepithelial tumors (Table 2). The average age and sex ratio of responders were not significantly different from those of the non-responders (Table 3). Most of the responders had a Karnofsky performance of ≧60 (Table 3). The levels of white blood cell count, red blood cell count, Hb, thrombocyte count, serum LDH, serum CRP, serum creatinine and BUN in responders were the same as those in non-responders (Table 3). Although these patients did not show any significant difference in respective ESR, ESR tended to be increased more frequently in responders (Table 3). After chemotherapy, the response of one patient was CR and that of 5 patients was PR, giving a response rate of 40%. The average age of the patients whose response was CR or PR was not significantly different from that in patients whose response was SD or PD (Table 4). Cases with a Karnofsky's rating

Table 4. Results of chemotherapy according to age, sex, performance status and tumor characteristics

Variables		CR+PR (1) (5)	SD+PD (1) (8)
Mean age±S.E.		70±6	72±2
Sex(male : female)		5 : 1	6 : 3
Performance status	60≦	5	4
	60>	1	5
Tumor characteristics			
TCC		6	8
Squamous cell carcinoma		0	1
Grade	II	2	0
	III	4	9
TNM classification	$Tis-T_2$	2	2
	T_3-T_4	4	7
	N_0	4	2
	N_1-N_2	1	2
	N_3-N_4	1	5
	M_0	4	2
	M_1	2	7

( ) : Number of patients.

above 60 were highly improved by chemotherapy. Two of the 5 cases showing a CR or PR, were grade II tumors, while only 4 of the 13 cases of grade III tumors showed a PR. Patients with histologically high stage tumors or patients with metastatic tumors experienced SD or PD in 7 of 11 cases or 7 of 9 cases, respectively (Table 4). Table 5 shows the results of chemotherapy in advanced urothelial tumor. Although remarkable regression occurred in a patient with pulmonary metastasis, the frequency of CR + PR was not significantly different from that of SD + PD. Two CDDP schedules combined with ADM and CTX or given concurrently with 5-FU appeared to decrease tumor size in some cases. Side effects, however, were frequent in patients receiving combination chemotherpy including CDDP.

DISCUSSION

Complete removal of a tumor demands careful assessment and planning for each case. The aim of total cystectomy is to remove the neoplastic lesion along with a wide margin of surrounding tumor-free tissues. According to Koss et al.[7], ten patients with bladder tumor who received cystectomy because of failure to respond to local therapy, had evidence of epithelial hyperplasia, atypical hyperplasia and non-papillary carcinoma *in situ* in regions adjacent to and remote from the obvious tumors. In addition, about 50% of non-selected patients with grade III primary bladder cancer had urothelial dysplasia far from the distinct neoplasm[8]. These reports suggest that widespread urothelial disease is common in patients with advanced bladder tumors. Subsequently, radical operation seems to be reasonable to obtain an objective response. Although the operative mortality is not higher than that after cystectomy alone with a difference of between 3 and 12%[9], the reported mortality after cystectomy increased significantly in patients over 65 years[9,10]. In this study, the mean age of the responders and that of non-responders was similar for all the patients receiving various treatments (Table 3) and for the subjects receiving chemotherapy (Table 4). In our study, two of the patients with grade II urothelial tumors responded to some treatment, but the majority of the patients with grade III urothelial tumors failed to respond to any kind of chemotherapy (Table 4). The greatest improvement in survival rate was seen for low stage cases particularly in patients without distant metastasis (Table 4). Cancer patients often present late in their biological life with overt evidence of metastatic foci already established. In such cases, surgical treatment as well as chemotherapy

Table 5. Results of chemotherapy and its side effects in patients with advanced urothelial tumors

Drugs	Response to chemotherapy		Side effects
	CR(1)+PR(5)	SD(1)+PD(8)	
5-FU(1200mg/day) for 30-34days	2	3	Anemia 1
Hyperthermia(120mg/day of bleomycin or 100mg/day of pepleomycin for 10days)	0	2	
CDDP(30-50mg/m^2) (day 1) ADM(30-50mg/m^2) (day 1) CTX(200-500mg/m^2) (day 2)	2	1	Leucopenia 2, Anemia 3, Thrombocytopenia 1.
MMC(4mg)+ADM(10mg) once a week for 8weeks	1	1	
CDDP(30-50mg/m^2) for 2-3cures 5-FU(1200mg/day) for 30days	1	0	Renal dysfunction 1.
Others	0	1	

Anemia : Fall in Hb>2g/dl, Leucopenia : white blood cell count<$3\times10^3/mm^3$, Thrombocytopenia : Thrombocyte<$30\times10^3/mm^3$, Renal dysfunction : Up in BUN>10mg/dl or serum creatinine>1.
( ) : Number of patients.

may only be palliative. Interestingly, 11 of the 15 patients who had a high score on the Karnofsky performance scale, responded with a CR or PR after chemotherapy. The general condition appears to be more important than age or laboratory biochemical data for obtaining a good therapeutic response. 5-FU was used adjuvantly to surgery and radiation therapy in the early 1960s. Randomized analysis suggested that the agent did not increase the survival rate but that it reduced the incidence of metastasis[11]. A similar therapeutic response was obtained in our study, but, combination chemotherapy of ADM and 5-FU in patients with advanced bladder cancer gave a 35% response rate[12]. The management of advanced bladder cancer with chemotherapy has been essentially palliative. In recent years, CDDP alone or in combination with other agents has been reported to be very effective[13]. Controversy continues as to the exact response of its administration methods. According to Yagoda[13,14], combination of CDDP with other drugs was not superior to CDDP alone. Schwartz and associates[15] used 3 to 4 courses of 250 mg/m^2 of CTX, and 45 mg/m^2 of ADM with 250 mg/m^2 of CDDP, and found that the 3-drug regimen was statistically superior to that of CDDP alone. Excellent synergistic action of such combinations have also been reported[16,17] A review of previous chemotherapy in patients with stage-D urothelial tract tumors showed that combinations of CDDP + ADM and vinblastine + methotrexate appear to be more effective than the agents administered singly[18]. We would like to emphasize that 3 of the 4 patients with locally advanced bladder tumor obtained objective response with 3/4 PR after combination chemotherapy including CDDP. In our study, combination chemotherapy with CDDP was tolerated by 3 patients. But it caused severe nausea, vomiting and anorexia, in one patient, making it necessary to discontinue therapy before the scheduled date. In addition, hematological or renal toxicity was often observed in the treated subjects. It is too anticipative to draw any conclusion because of the small number of patients and the short follow-up period. However, based on a comparison of the present results with a similar but non-randomized studies, combination chemotherapy inclusive of CDDP appears to be promising. Since recent attempts in therapy using various drugs in combination has shown that various drugs act synergistically against cancer, we believe that the evaluation of the effects of existing and new agents against transitional cell carcinoma will lead to the discovery of an effective chemotherapeutic regimen.

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和文抄録

進行性尿路上皮癌の治療経験

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23例の進行性尿路上皮腫瘍に対し，外科療法，化学療法，放射線療法をおこなった．放射線療法の有無にかかわらず，根治的外科手術により8例が tumor free になった．15例に対する化学療法で1例が，CR，5例が PR となった．low grade, low stage, Karnofsky performance rating が高い例に対しては高成績が得られた．CDDP, ADM, cyclophosphamide の三者併用療法，または CDDP 中心の化学療法は進行性尿路上皮腫瘍に対して有効であるように推測された．