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Combination chemotherapy for advanced bladder cancer with adriamycin, cyclophosphamide, and 5-fluorouracil

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Summary. *Combination three-drug chemotherapy with adriamycin (ADM), cyclophosphamide (CPM), and 5-fluorouracil (5-FU) was performed in 24 cases of advanced bladder cancer who underwent surgical treatment, and three cases with recurrent or metastatic bladder cancer. The average age (25 men and 2 women) was 53. Of the 24 cases, nine were in stage T2, 10 in T3, and five in T4.*

One course consisted of a combination of 30 mg/m² of ADM, 300 mg/m² of CPM, and, 250 mg of 5-FU, administered five times. The combination was administered to three groups: every day for 5 days consecutively in group A, twice a week for $2^1/_2$ weeks in group B, and once every 4 weeks for 16 weeks in group C. After injection of ADM, CPM, and 5-FU, 200 mg/day of 5-FU was administered PO daily in all three groups.

The 5-year survival rate of the 24 cases (apart from 3 cases with measurable metastatic tumor) was 58%. The 5-year survival rate for stage T2 was 88%, and that for stage T3 was 62.5%; all patients with stage T4 disease died before 3 years and 6 months. Partial response was seen in two out of three patients with recurrent or metastatic disease.

Alopecia was observed in all cases as a side-effect of the chemotherapy. Also anorexia, nausea, and myelosuppression were observed in many cases, though the degree was tolerable. However, there were no disorders of the cardiovascular system, except for one case with transient hypotension.

Introduction

While therapeutic results in advanced bladder cancer have gradually improved with the development of a variety of methods, results are not yet satisfactory. At Jikei University Hospital, we have combined radiation therapy and conservative surgery to treat advanced bladder cancer while preserving the bladder. As surgery and radiotherapy have only local effects, they are ineffective against distant metastases, and therefore have limitations in the treatment of advanced bladder cancer. To compensate for these limitations, since 1977 we have been using a three-drug combination chemotherapy as adjuvant therapy in addition to surgery and radiotherapy. We report here the results of combination chemotherapy with adriamycin (ADM), cyclophosphamide (CPM), and 5-fluorouracil (5-FU) in 27 patients with advanced bladder cancer over the past 5 years.

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Materials and methods

Twenty-four patients with urinary bladder cancer who received initial treatment with chemotherapy from January 1977 to May 1982, and three more patients with recurrent and metastatic bladder cancer were treated. These all had transitional cell carcinoma of grade 2 or higher and stage T2 or more according to the UICC classification. Twenty-five were male and two female, and their mean age was 53 years. Stage was determined by pelvic arteriography, CT, bimanual examination under anesthesia, TUR biopsy, etc. According to the WHO histological criteria, 14 showed grade 2 transitional cell carcinoma, nine had grade 3 transitional cell carcinoma, two had adenocarcinoma, and two more had undifferentiated carcinoma. Of the 24 patients who received initial treatment by adjuvant chemotherapy, nine had stage T2, 10 had stage T3 and 5, stage T4 disease, and all were NX and MO (Table 1). In 12 cases (50%), radiotherapy was used in addition to surgical therapy.

The combination chemotherapy consisted of 30 mg/m² of ADM, 300 mg/m² of CPM, and 250 mg of 5-FU. The regimen used was a single course of five doses each of ADM, CPM, and 5-FU, administered over 5 consecutive days in group A (three cases of grade 3 transitional cell carcinoma, one case of adenocarcinoma, and one of undifferentiated carcinoma, being two in T2, one in T3, and two in T4), twice weekly for a total of $2^1/_2$ weeks in group B (nine cases of grade 2 transitional cell carcinoma, six cases of grade 3 transitional cell carcinoma, and one case of undifferentiated carcinoma, being five in T2, six in T3 and two in T4), and in group C (four cases of grade 2 transitional cell carcinoma, one case of grade 3 and one case of adenocarcinoma, being two in T2, three in T3, and one in T4) at 4-week intervals for 16 weeks. After completion of one or

Table 1. Histologic type and stage in 24 cases receiving initial chemotherapy

Hist. type	Stage			
	T2	T3	T4	
TCC G2	7	4	0	11
TCC G3	2	5	2	9
Adenocarcinoma	0	0	2	2
Anaplastic Ca	0	1	1	2
	9	10	5	24

two courses, 200 mg/day 5-FU was administered PO for 2 years. For recurrent cases, chemotherapy was employed twice weekly.

The results of the combination chemotherapy were evaluated by determining the actuarial survival rate for the 24 patients receiving initial treatment and the responses of lesions in the three cases of recurrent and/or metastatic disease. In addition, side-effects of chemotherapy, if any, were evaluated in all cases treated.

Results

1. Results in patients receiving initial treatment

As a result of the adjuvant therapy in 24 cases, the actuarial 5-year survival rate for nine patients in stage T2 was 88%, and that for 10 patients in stage T3 was 62.5%. All the patients in stage T4 died within 3 years and 6 months, and their mean survival time was 17 months (Fig. 1).

The actuarial 5-year survival rates in transitional cell carcinoma were 77% for 11 grade 2 patients and 60% for nine grade 3 patients (Fig. 2).

The survival rates according to regimens were: 57% at 3 years and 6 months in group A, 83.3% at 5 years in group B, and 50% at 5 years in group C (Fig. 3). Although group B patients showed the best survival rate, there was no statistically significant difference among these groups.

2. Results in recurrent and/or metastatic disease

Three patients with recurrence and measurable metastatic lesions were treated by twice-weekly administration. Case 1 had a metastatic lymph node, 4 × 3 cm in size, in the neck and another, 3 × 2 cm in size, in the inguinal region before chemotherapy. These tumors began to shrink in size from the 2nd week of treatment, and by the 4th week of administration they were fibrotic and barely palpable, and were no larger than 5 mm. Oral administration of 5-FU was continued, but from about the 8th week of treatment the metastatic lymph nodes increased in size, and the patient died 1 year later.

Case 2 showed a relapsed non-mobile tumor 18 × 12 cm in size at the surgical wound after total cystectomy. Combination chemotherapy twice weekly resulted in regression of the tumor after 1 week of treatment, and by the 3rd week the tumor had become mobile and shrunk to 8 × 6 cm in size. After 8 weeks of treatment tumor resection was performed.

In both the above cases, tumor regression by 50% or more continued for more than a month, and the responses were classified as partial remission in accordance with the criteria of Koyama and Saito.

The therapeutic results for the three cases of recurrent/metastatic disease with measurable lesions are summarized in Table 2. According to Karnofsky's criteria, they were 1-B, 1-A, and 0-0, and according to the criteria of Koyama and Saito combination chemotherapy was effective in two of these cases.

3. Side-effects

Table 3 shows the incidence of side-effects. Alopecia was observed in all cases, while anorexia occurred in 93% of the patients, leukopenia in 37%, and thrombocytopenia in 30%. The side-effects appeared most prominently in group A, in which patients received drugs on 5 consecutive days. Transient elevation of GOT and GPT were seen in three cases in group A. Cardiovascular upset was seen in only one case in the present study, and took the form of transient hypotension only. The most serious clinical side-effect encountered in the present study was leukopenia, as four of the treated patients showed severe leukopenia at a level of 1,000 cells/mm^3 or less

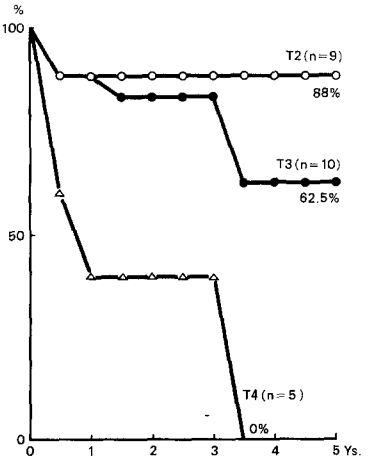

Fig. 1. Actuarial survival by clinical stage

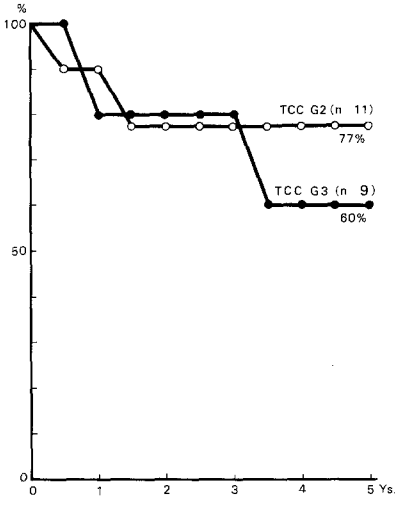

Fig. 2. Actuarial survival by pathological grading

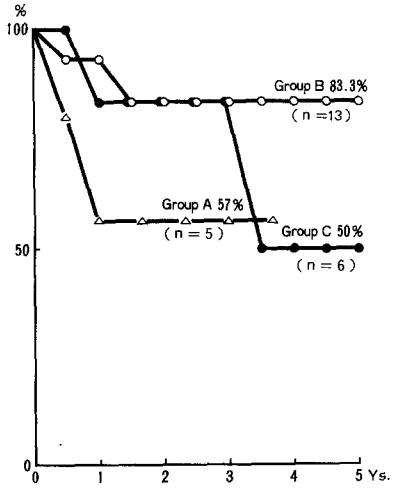

Fig. 3. Actuarial survival according to treatment regimen

Table 2. Tumor response to ACF chemotherapy in measurable metastatic disease

			Site	Before	After	Karnofsky	Koyama Saito
1.	O.M 50	TCC G3 M	Neck L.N. Inguinal L.N.	4 × 3 3 × 2	1 × 0.5 0.8 × 0.5	1-B	PR
2.	N.T 60	TCC G3 M	Abdominal tumor	18 × 12	8 × 6	1-A	PR
3.	S.S 63	TCC G2 M	Abdominal tumor	15 × 14	15 × 14	0-0	NC

Table 3. Side-effects of ACF chemotherapy

		Cases	%
1. Cardiovascular	ST ↑ ↓	0	0
	Hypotension	1	3
2. Haematological	WBC (< 3,000)	10	37
	Platelet (< 100,000)	8	30
3. Skin	Alopecia	27	100
4. Gastrointestinal	Appetiteloss	25	93
	Nausea	7	26
5. Mouth	Ulcer	6	22
6. Liver	GOT, GPT ↑	3	11
7. Kidney	BUN, Cr ↑	0	0
8. Fever		0	0

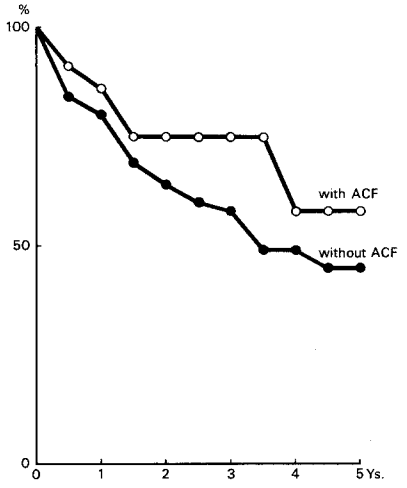

Fig. 4. Actuarial survival of all cases with or without ACF chemotherapy

(Fig. 4). One of the patients in group A died of leukopenia and ensuing infection as a consequence of the combination chemotherapy on the 10th day of treatment.

Discussion

Although the results of treatment for superficial bladder cancer have shown marked improvement during recent years [6], those for advanced bladder cancer remain unsatisfactory. In spite of radical total cystectomy and adjuvant radiotherapy, the 5-year survival rate for advanced bladder cancer has never exceeded 40% [5, 7]. For this reason, systemic chemotherapy is considered mandatory for those patients with bladder tumors who show the slightest signs of progressive disesase or who are suspected of showing recurrence or metastases. The role of chemotherapy in the treatment of bladder cancer has not yet been established, but during recent years some promising results have been reported [2, 4].

To obtain better results in advanced bladder cancer, the authors combined ADM, CPM, and 5-FU, each of which is considered relatively effective against bladder cancer [1, 3, 8], so as to expand the anticancer spectrum and maximize mutual potentiation while minimizing side-effects.

The efficacy of combination chemotherapy was evaluated by determining the survival rates for advanced bladder cancer patients with cell differentiation of grade 2 or higher and in stage T2 or over who were initially treated with chemotherapy. The 3-year survival rate of 77% and 5-year survival rate of 59% in cases treated with combination chemotherapy were significantly higher than the 3-year survival rate of 72% and 5-year survival rate of 46% for same-stage patients treated in our hospital during the same period using conventional methods of treatment but without chemotherapy (Fig. 4). Because of the relatively small number of patients in each of the three regimen groups in the present study, no statistically significant difference was noted among the groups in terms of their survival rates.

The results of combination chemotherapy in three patients with recurrent and measurable metastatic lesions showed the antitumor effect of this therapy (twice weekly for a total of 5 doses) in two of the three cases.

The efficacy of the three-agent combination chemotherapy with ADM, CPM, and 5-FU in the present study was more impressive than the results of our previous experience with multiple-agent chemotherapy using mitomycin C, 5-FU, and cytosine arabinoside for advanced bladder cancer.

Side-effects of this combination chemotherapy, such as alopecia and leukocytopenia, appeared in many of the treated patients but were tolerated well by most patients. The above results show that this combination chemotherapy, using ADM as the principal drug, is a useful therapy for urinary bladder cancer.

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