Cancer Chemother Pharmacol (1987) 20 (Suppl): S 34–S 38

Cancer Chemotherapy and Pharmacology

Postoperative systemic adjuvant chemotherapy for bladder cancer

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Summary. Forty-six patients with bladder cancer without distant metastasis (M_0) were treated by chemotherapy as an adjuvant after total cystectomy using three protocols (protocol I: adriamycin 50 mg/m^2, cyclophosphamide 500 mg/m^2, and *cis*-platinum 50 mg/m^2 i.v., starting at least 2 weeks after surgery every 3 weeks for three cycles; protocol II: adriamycin 30 mg/m^2 on the 1st postoperative day, cyclophosphamide 300 mg/m^2 on the 1st and the 7th days; protocol III: FT-207 60 mg/m^2, p.o. every day for 1 year).

Average follow-up periods after surgery by protocol were 18 months for protocol I, 31 for protocol II, and 43 for protocol III. Analysis of the survival curves showed no statistically significant differences among the three groups or between a historical control group of 106 patients and the entire patient population examined in the present study. The histopathological grades recorded in the 46 patients were G_1, G_2, and G_3 in 1, 22, and 23, respectively. However, from a study of 48 pT_3 and pT_4 cases, the survival rate of 10 patients receiving protocol I therapy was statistically significantly higher than those of 12 patients treated according to protocol II and of 26 historical controls, at 1 year and 2 years, respectively. Toxic effects, with gastrointestinal symptoms including nausea and vomiting and myelosuppression (including leukopenia and anemia) were more frequent with protocol I. Alopecia occurred in about 80%–90% of patients treated according to either protocol I or II. Almost all patients could tolerate adjuvant chemotherapy, and none of them died as a result of these regimens. The results recorded in this study justify the evaluation of combination adjuvant chemotherapy with adriamycin, cyclophosphamide and *cis*-platinum in a prospectively randomized trial.

Introduction

Many reports have suggested that survival of patients with invasive bladder cancer is not satisfactory following total cystectomy; the 5-year survival rates after surgery have ranged from zero to 25% [14]. Preoperative radiotherapy has been added by many investigators, but this has improved the survival rate only slightly (highest published, 20% at 5 years) [1, 13, 17]. Because of this, the possibility that undetected micrometastases may already be present at the time of primary treatment was pointed out [9, 12], leading to recognition of the need for systemic chemotherapy.

Recently, although different postoperative adjuvant chemotherapy regimens have been reported by many authors, the results of their evaluation are equivocal. In the present study, adjuvant chemotherapy according to three protocols was administered to 46 patients with bladder cancer after total cystectomy, and the survival rates were calculated for each protocol.

Patients and methods

The study included 46 patients who had undergone cystectomy for primary bladder cancer and were treated with postoperative adjuvant chemotherapy between January 1978 and December 1985. Their clinical and pathological details are shown in Table 1. The male:female ratio was

Table 1. Clinical and pathologic details of patients

Characteristics		Protocol and number of patients		
		I ($n = 10$)	II ($n = 31$)	III ($n = 5$)
Mean age	(Years)	58.5	59.7	59.4
	(Range)	(47–72)	(33–74)	(54–68)
Sex	Male	7	26	5
	Female	3	5	0
Average duration of protocol and follow-up	(Months)	18	31	43
	(Range)	(2–45)	(3–56)	(6–78)
Pathologic findings				
Grade	1	–	–	1
	2	4	15	3
	3	6	16	1
Stage	pT_{is}	–	4	–
	pT_a	–	–	1
	pT_1	–	11	–
	pT_2	–	4	2
	pT_{3a}	3	4	–
	pT_{3b}	4	7	–
	pT_4	3	1	2
Cell type	TCC	7	30	4
	SCC	2	1	1
	AC	1	–	–

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38:8, and the mean age was 59 years (33–74). The tumors of all patients originated from the bladder and all had been treated by total cystectomy and urinary diversion. None of the patients received radiotherapy. Of the tumors, 41 were transitional cell carcinoma, 4 were squamous cell carcinoma and 1 was adenocarcinoma, pathologically. The histopathological grading of the tumors was G_1, G_2 and G_3 in 1, 22 and 23 cases, respectively, and the tumor stage was pT_{is}, pT_a, pT_1, pT_2, pT_3, T_4 in 4, 1, 11, 6, 7, 11, and 5 cases, respectively.

All patients were examined before starting chemotherapy and at weekly intervals until 1 month after completion of the planned treatment, the following studies being carried out in each: physical examination, blood and platelet count, routine blood chemistry profile, urinalysis, 24-h creatinine clearance, ECG, etc. to check side effects. The adjuvant chemotherapy was performed according to three protocols (Table 2). Protocol I consisted of adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 i.v. on day 1 and *cis*-platinum (CDDP) 50 mg/m^2 i.v. on days 2–3. In protocol II, adriamycin 30 mg/m^2 was given i.v. on day 1 in combination with cyclophosphamide 300 mg/m^2 i.v. on day 1 and day 7. In protocol III, only a single drug, FT-207 was given p.o. Protocol I was started at least 1–2 weeks after the operation. Protocol II was performed on postoperative day 1 with one course, and protocol III was continued for 1 year starting as soon as the patients were able to take the drug p.o. after the operation.

Starting 24 h before the administration of CDDP, patients were hydrated by infusion of 1000–1500 ml 5% dextrose in normal saline i.v. fluid, followed by i.v. infusion of 12.5 g mannitol and 20 mg furosemide i.v. Then 50 mg/m^2 CDDP mixed in 500 ml 5% dextrose was given i.v. over 4 h, followed by 2000–2500 ml fluids and electrolytes over 6 h according to urine output. As an antiemetic drug we gave metoclopramide or domperidone just before giving CDDP. All patients were followed up until evidence of tumor recurrence. Survival curves were created by the actuarial method of Kaplan and Meier.

Table 2. Adjuvant chemotherapy protocols for bladder cancer associated with total cystectomy

Protocol I	Day 1	ADM	50 mg/m^2 i.v. (push)
		CPM	500 mg/m^2 i.v. (push)
	Day 2	CDDP	50 mg/m^2 i.v. (drip)
Every 3 weeks for three cycles			
Protocol II	Day 1 (1st postoperative day)		
		ADM	30 mg/m^2 i.v. (push)
		CPM	300 mg/m^2 i.v. (push)
	Day 7	CPM	300 mg/m^2 i.v. (push)
Every 3 weeks (once)			
Protocol III	FT-207 (tegafur)		600–800 mg/day p.o. for 1 year

ADM, adriamycin; CDDP, *cis*-platinum; CPM, cyclophosphamide

Results

Survival rates of all cases

Figure 1 displays the survival curves constructed for four groups of the patients, each of whom received one of the three protocols described or no adjuvant chemotherapy at all. As a result of adjuvant chemotherapy in 46 cases, the

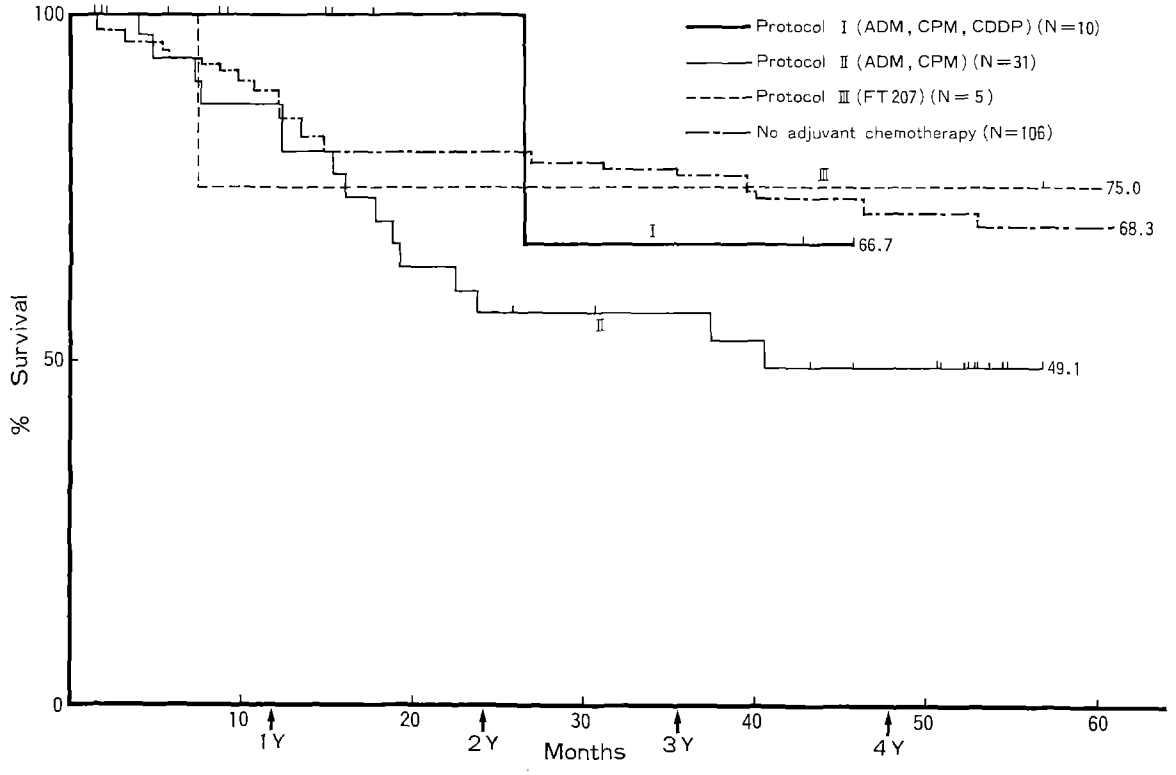

Fig. 1. Survival of all patients according to treatment regimen

survival rates were 100% at 1 year and 68% at 3 years for protocol I, with corresponding rates of 90% and 56% for protocol II and 75% and 75% for protocol III, while in the no chemotherapy group, the survival rate was 87% at 1 year and 77% at 3 years.

The mean follow-up (still alive or until death) in the four groups was 18 months (range 2–45 months) for protocol I, 31 months (3–56 months) for protocol II, 43 months (6–78 months) for protocol III, as shown in Table 1, and 45 months (6–85 months) in the no chemotherapy group. As shown in Fig. 1, the survival curves of all four groups were similar, and analysis of the survival curves showed no statistically significant differences among the four groups.

Survival rates of patients with pT_3 or less advanced disease

The survival curves in the three groups of 48 patients in all who were treated according to protocol I (10 cases) or protocol II (12 cases) or not receiving chemotherapy (26 cases) and whose pathological stage was pT_3 or less are shown in Fig. 2. The survival rates of these patients were 100% at 1 and 2 years and 68% at 3 years for protocol I, and 70% at 1 year and 42% at both 2 and 3 years in protocol II. In the no chemotherapy group the survival rate was 68% at 1 year and 50% at 3 years. By analyzing the survival rates of three groups by standard errors, the survival rate of the patients in protocol I was statistically higher than the survival rates of patients receiving protocol II and no adjuvant chemotherapy at 1 year and 2 years from the operation date, respectively. There was no statistical difference between the survival rate of the patients receiving protocol II and that of the patients receiving no chemotherapy. Recently we have applied only protocol I for pT_3 or pT_4 $N_{0-3}M_0$ bladder cancer who underwent radical cystectomy. The pathologic findings, the number of cycles of the regimen, and the outcome in 10 patients who received chemotherapy according to protocol I are shown in Table 3. Four patients could not be given three cycles of protocol I chemotherapy: patient 9 received only one cycle because of hepatitis, patients 2 and 8 received only two cycles because of severe myelosuppression, and patient 10 received only two cycles because of cardiovascular disturbance. There 8 of these 10 patients still alive without evidence of disease, and the average survival is 18 months (range 4–45).

Toxic effects

The incidence of toxic effects according to each protocol is listed in Tables 4 and 5. Myelosuppression was very frequent both leukocytopenia and anemia occurring in 90% of the patients in the protocol I group, and thrombocytopenia occurred in 80% of these patients. In the patients treated according to either protocol II and protocol III, myelosuppression occurred less frequently than with protocol I (Table 4). The most common toxic non-myelosuppressive effects were gastrointestinal toxicity and alopecia. Gastrointestinal toxicity, including anorexia, nausea, and vomiting, occurred in 100% of the patients treated according to protocol I. Vomiting and severe nausea were observed more often in patients treated with protocol I, which included CDDP, than with protocol II, but were controlled by antiemetic drugs.

Alopecia probably caused by adriamycin developed in 90% of the patients treated with protocol I and in 77% of those with protocol II. No patients died of the toxic effects of any of the three protocols.

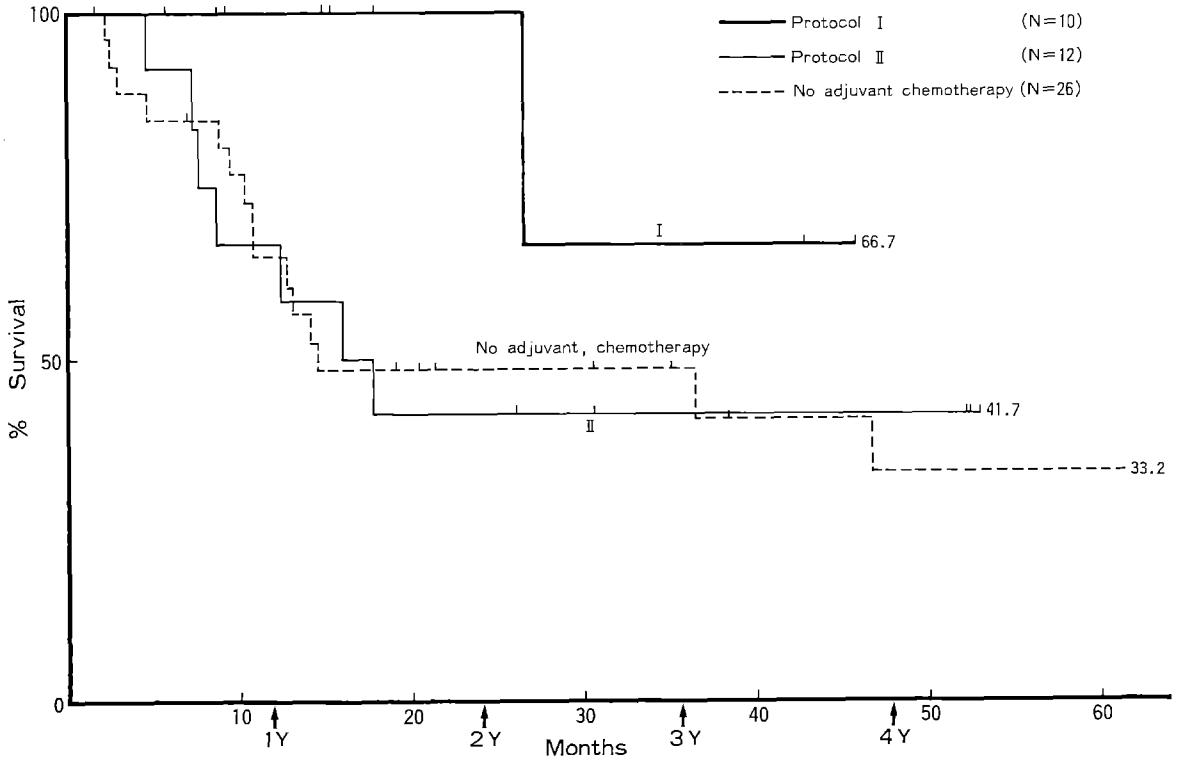

Fig. 2. Survival of patients with advanced disease ($\geqq pT_3$)

Table 3. Adjuvant chemotherapy with ADM, CPM, and CDDP

No.	Age	Sex	Cell type	Grade	Stage	pN	No. of drug courses	Outcome
1	51	M	AC	G_2	pT_{3b}	pN_0	3	26M Died of cancer
2	62	M	TCC	G_3	pT_{3b}	pN_0	2	45M Alive with NED
3	68	F	SCC	G_2	pT_{3b}	pN_1	3	42M Alive with NED
4	52	M	TCC	G_3	pT_4	pN_1	3	18M Alive with NED
5	61	M	TCC	G_2	pT_{3b}	pN_1	3	15M Alive with NED
6	56	M	TCC	G_3	pT_4	pN_2	3	14M Alive with NED
7	47	M	TCC	G_2	pT_{3b}	pN_1	3	9M Alive with NED
8	49	F	SCC	G_2	pT_4	pN_3	2	9M Alive with cancer
9	72	M	TCC	G_3	pT_{3a}	pN_2	1	5M Alive with NED
10	67	F	TCC	G_3	pT_{3b}	pN_0	2	4M Alive with NED

NED, no evidence of disease

Table 4. Myelotoxicity

Myelotoxic effects		Protocol and number of patients		
		I ($n = 10$)	II ($n = 31$)	III ($n = 5$)
Leukocytopenia ($< 3000/mm^3$)	(%)	9 (90)	17 (55)	0
Median		1300	1700	
Range		650–2200	400–2900	
Thrombocytopenia ($< 100 \times 10^3/mm^3$)	(%)	5 (50)	3 (10)	0
Median		590	930	
Range		320–980	920–980	
Anemia ($< 3.5 \times 10^6/mm^3$)	(%)	9 (90)	9 (29)	1 (20)
Median		318	306	306
Range		285–348	250–338	306

Table 5. Non-myelosuppressive toxicity

Side effects	Protocol and number of patients		
	I ($n = 10$)	II ($n = 31$)	III ($n = 5$)
Anorexia	10 (100%)	20 (65%)	0
Vomiting	10 (100%)	6 (19%)	0
Alopecia	9 (90%)	24 (77%)	0
Hepatic effects	2 (20%)	7 (23%)	0
Cardiovascular effects	1 (10%)	1 (13%)	0
Fever, infection	2 (20%)	13 (42%)	0

Discussion

Because it has been pointed out that micrometastases of invasive bladder tumors might persist, after radical cystectomy, the administration of systemic adjuvant chemotherapy is now regarded as a possible way of improving survival in these patients. Recently, the number of reports concerning adjuvant chemotherapy with radiotherapy and/or surgery have increased, but none has clearly documented improved survival of patients as a result of adjuvant chemotherapy. One reason for this is the lack of successful systemic chemotherapeutic modality studies for metastatic bladder cancer, because phase II studies have shown a low incidence of complete remission with combination therapy [6, 16]. The second reason is that it is difficult to obtain significant statistical analysis, because of the small number of patients entered in studies and because many studies were not randomized trials.

Hall et al. [3] reported that combination therapy using adriamycin, bleomycin, 5-fluorouracil and methotrexate was ineffective in 10 $T_3N_{0-1}M_0$ bladder cancer patients after radiation therapy and radical cystectomy with long-term follow-up, although the results obtained with this combination in metastatic disease showed considerable antitumor activity. Clyne et al. [2] reported that adjuvant chemotherapy with adriamycin and 5-fluorouracil for 12 patients with stage T_3 bladder tumors after TUR did not improve the survival over that in a historical control group. Richards et al. [10] also used adriamycin and 5-fluorouracil as adjuvant chemotherapy in 129 $T_3N_XM_0$ bladder cancer patients undergoing radical radiotherapy in a randomized prospective trial, but the addition of this form of chemotherapy did not influence survival. Methotrexate is recognized as an effective drug for transitional cell carcinoma of bladder. Oliver [8] suggested that the results of the study of methotrexate as adjuvant therapy were encouraging and proposed a prospective randomized trial. A randomized trial of adjuvant chemotherapy using methotrexate for T_3 carcinoma of the bladder treated with radiotherapy and/or total cystectomy is being tried by Williams (Co-operative Urological Cancer Group of England [15]), but no conclusion on survival has yet been obtained. As for combination adjuvant chemotherapy consisting of adriamycin and cyclophosphamide after total cystectomy, as with our protocol II, Merrin and Beckley [7] commented on the usefulness of this chemotherapeutic therapy according to the results in 25 patients, but there have been no reports concerning this regimen since. A randomized study with combination chemotherapy including CISCA or CDDP and at least two other drugs for stage pT_3 or pT_4 and/or node-positive disease after radical cystectomy was performed by Skinner et al. [11]; they commented that adjuvant chemotherapy appeared to result in a slight delay in time to relapse, but that no influence on overall survival was observed.

In the Japanese literature, Kakizoe and Matsumoto [5] recently reported combination adjuvant chemotherapy using neocarzinostatin, cyclophosphamide, and vincristine for pT_3 and pT_4 bladder cancer patients. The survival curve of T_3 and T_4 patients receiving this regimen after radical cystectomy was above that of the historical control group,

and this difference was significantly significant. Before CDDP was available, the authors performed adjuvant chemotherapy according to protocol II and protocol III. Although combination chemotherapy with protocol II (adriamycin + cyclophosphamide) was given from the 1st postoperative day, the actual dose of two drugs was small and only one cycle of drug was administered, resulting in a low rate of side effects. However, this protocol proved not effective in terms of improvement of survival. Protocol III (FT-207: with lower toxic effects) was performed over a long period (1 year) but also appeared ineffective. Recently, we have applied only protocol I (adriamycin + cyclophosphamide + *cis*-platinum) in cases with $pT_3N_{0-3}M_0$ carcinoma of the bladder after radical cystectomy. This regimen has been most frequently used in metastatic bladder cancer, and the antitumor activity is reported to be relatively high [4, 6, 16]. Even though the period of follow-up is short, the results obtained with protocol I are better than those with protocol II or protocol III or with no chemotherapy. Of our 10 cases, 8 are still alive without evidence of disease and none has died of toxic effects. With careful management, this regimen can be applied satisfactorily. Although it is difficult to draw conclusions from this small non-randomized study after the short follow-up period, protocol I (three-drug combination chemotherapy with adriamycin, cyclophosphamide and *cis*-platinum) appears to be effective as an adjuvant therapy for invasive bladder cancer. We are therefore currently conducting large-scale clinical trials with this regimen in controlled prospective studies.

Acknowledgement. The work described in this paper was supported in part by a Grant-in-Aid (61–23) for Cancer Research from the Ministry of Health and Welfare of Japan.

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