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Phase III trial of The Japanese Urological Cancer Research Group for Adriamycin: cyclophosphamide, adriamycin and cisplatinum versus cyclophosphamide, adriamycin and 5-fluorouracil in patients with advanced transitional cell carcinoma of the urinary bladder

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Summary. A non-randomized clinical study on systemic combination chemotherapy was conducted by the Japanese Urological Cancer Research Group for Adriamycin to compare the effectiveness of CAP (cyclophosphamide 200–500 mg/m^2, adriamycin 30–50 mg/m^2 and cisplatin 30–50 mg/m^2) and CAF (cyclophosphamide 200–500 mg/m^2, adriamycin 30–50 mg/m^2 and 5-fluorouracil 250 mg/m^2) in 123 patients (104 evaluable) with advanced and/or metastatic cancer of the urinary bladder. Among 96 patients who were non-randomly selected to receive CAP, 4 achieved complete remission, 12 achieved partial remission, 7 achieved minor response, 30 had stable disease, and 43 had disease progression. The response in the 8 patients who received CAF were: partial remission in 1 and progressive disease in 7. The overall response rate to CAP therapy was 17%, as against 13% for CAF therapy. The median duration of survival with CAP was 29 weeks and with CAF, 22 weeks. The differences between the two groups in duration of survival and response rate were not statistically significant. Complete and/or partial remissions were observed in the lymph nodes, lung and liver in 32%, 24%, and 57% of cases, respectively. There was no objective response in bone metastasis. The main side effects of CAP were anorexia (88%), nausea and/or vomiting (81%), alopecia (65%), leukopenia (72%), anemia (48%), and renal dysfunction (17%). No patients died as a result of toxicity of these combination chemotherapy modalities.

Introduction

The prognosis for patients with advanced urothelial transitional cell carcinoma is dismal and is only minimally altered by current treatment modalities. Systemic chemotherapy has usually been used in the treatment of locally advanced or metastatic urothelial carcinoma not amenable to surgical resection and/or radiotherapy. Many regimens of single or combined administration of chemotherapeutic agents have been found to be active against advanced urothelial carcinoma. The reported response rates to adriamycin vary from 10% to 40% [3, 6, 8, 15, 18, 28]; the response rate to methotrexate ranges from 24% to 43% [6, 20]; the response rate to cisplatin ranges from 20% to 46% [19, 23, 24, 28, 29]; the response rate to 5-FU ranges from 27% to 39% [3, 6, 8, 22]. With the most common non-cisplatin combination, 5-FU and adriamycin, the response rate was from 35% to 40% [5, 7], and that with 5-FU, cyclophosphamide and adriamycin (CAF) was from 0 to 18% [11, 14, 22]. On the other hand, the most common cisplatin combinations were cisplatin + cyclophosphamide, and cyclophosphamide + adriamycin + cisplatin (CAP), and the overall response rates were from 12% to 61%, and from 13% to 83%, respectively [1, 2, 10, 11, 16, 17, 21, 24, 25, 27, 28, 29]. Combinations of chemotherapeutic drugs in advanced urothelial carcinoma have yielded varying response rates, which have not clearly demonstrated their superiority over single agents but seem to yield a longer duration of response and survival. However, these remissions were of short duration. The present study was a prospective multi-institutional non-randomized trial comparing CAP and CAF in patients with advanced and/or metastatic transitional cell carcinoma of the urinary bladder.

Table 1 lists the members of the Japanese Urological Cancer Research for Adriamycin, chaired by Prof. Tadao Niijima, MD of the University of Tokyo, Japan, who organized this clinical trial.

Offprint requests to: A. Maru

Table 1. The Japanese Urological Cancer Research Group for Systemic Combination Chemotherapy (Chairman: Tadao Niijima, MD)

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Aomori Prefectural Central Hospital	(K. Yamato, MD)
Iwate Medical University	(T. Ōhori, MD)
Iwate Prefectural Central Hospital	(I. Yoshida, MD)
Tohoku University	(S. Orikasa, MD)
Yamagata University	(K. Suzuki, MD)
Niigata Cancer Center	(Y. Sakata, MD)
Saitama Central Hospital	(Y. Ishii, MD)
University of Tsukuba	(K. Koiso, MD)
Chiba University	(J. Shimazaki, MD)
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University of Tokyo	(T. Niijima, MD)
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Showa University, Fujigaoka Hospital	(Y. Kai, MD)
First Hospital of Nippon Medical School	(Y. Nakagami, MD)
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Nagoya City University	(K. Ohtaguro, MD)
Nagoya University	(H. Mitsuya, MD)
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Japanese Red Cross Nagoya Second Hospital	(K. Obata, MD)
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Osaka Medical College	(S. Miyazaki, MD)
Kobe University	(S. Kamidono, MD)
Kobe City General Hospital	(M. Matsuo, MD)
Toyama Medical and Pharmaceutical University	(T. Katayama, MD)
Okayama University	(H. Ōmori, MD)
Kawasaki Medical School	(H. Tanaka, MD)
Tottori University	(H. Goto, MD)
Hiroshima University	(H. Nihira, MD)
Kochi Medical School	(Y. Fujita, MD)
University of Tokushima	(K. Kurokawa, MD)
Shikoku Cancer Center	(T. Uyama, MD)
Ehime University	(M. Takeuchi, MD)
Kyushu University	(J. Kumazawa, MD)
Kurume University	(K. Eto, MD)
Nagasaki University	(Y. Saito, MD)
Medical College of Oita	(J. Ogata, MD)
Kagoshima University	(Y. Ohi, MD)

Materials and methods

Between 1 September 1983 and 31 December 1985, a total of 123 patients with locally advanced and/or metastatic transitional cell bladder carcinoma or who had failed previous surgery, chemotherapy and/or radiotherapy, were entered in the study. They all had measurable and/or evaluable lesions detected by physical examination, chest X-ray, intravenous urography, liver and bone scans, computerized tomography (CT) and cystoscopy. All patients were evaluated initially and at weekly intervals, the following studies being performed in each: physical examinations, body weight and height, complete blood and platelet count, routine chemical profile, urinalysis, 24-h urine creatinine clearance, electorcardiogram, 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 study was not randomized and was limited to patients under 80 years of age. Patients who had received other therapeutic modalities, such as systemic chemotherapy, immunotherapy, and radiotherapy 3 weeks or less before were excluded. Originally 123 patients were included in the present study, but 19 dropped out; thus, 77 male and 27 female patients, totalling 104 cases, were evaluable. The 19 patients excluded from the evaluation were ineligible due to protocol violation, early death, or failure to attend for follow-up. The median age was 62 years, with a range of 34–79 years. Prior treatment for the primary tumors was ascertained in 90 patients; 81 patients had undergone surgery; 28 patients, radiotherapy; and 42 patients, chemotherapy. Primary lesions included pulmonary metastasis in 45 patients, regional or peripheral lymph nodes (iliac, para-aortic and supuraclavicular) in 34 patients, bladder tumors in 29, local extension in 4 patients, bone metastasis in 28, liver metastasis in 7, and others in 2 (Table 2).

The combination chemotherapy was performed according to two protocols. Arm I received 30–50 mg/m^2 adriamycin i.v. on day 1, 200–500 mg/m^2 cyclophosphamide i.v. on day 1, and 250 mg/m^2 5-fluorouracil i.v. on day 1 or 2. In arm II, 30–50 mg/m^2 adriamycin was given i.v. on day 1 in combination with 200–500 mg/m^2 cyclophosphamide i.v. on day 1 and with 30–50 mg/m^2 cisplatin i.v. on day 2. Before the i.v. administration of 30–50 mg/m^2 cisplatin on day 2 the patients were prehydrated with dextrose in normal saline and mannitol, and additional i.v. fluids were administrated for 6–8 h. These courses were repeated every 3 or 4 weeks. An 'adequate' trial case was

Table 2. Patient characteristics

Characteristics	CAP	CAF	Total
Sex			
Male	71	6	77
Female	25	2	27
Average age	61.7	61.9	61.7
Range	34–79	49–72	34–79
Primary	37	4	41
Recurrent	59	4	63
Previous therapy			
Surgery	81	7	88
Chemotherapy	41	4	45
Radiotherapy	28	2	30
No treatment	13	1	14
Sites of measurable disease			
Lung	42	3	45
Lymph nodes	31	3	34
Bladder tumor	28	1	29
Bone	26	2	28
Liver	7	0	7
Local extension	3	0	3
Skin	2	0	2
Adrenal gland	1	0	1

defined as any case of a patient who received at least one course and survived for more than 1 month. Patient response was classified as follows: complete remission (CR), disappearance of all objective parameters; partial remission (PR), 50%–99% decrease in the sum of the products of two diameters of all measurable 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 lesion. Overall objective response rate was included in CR and PR. Duration of response and survival were calculated from the onset of treatment. Toxicity was recorded when BUN was over 25 mg/dl, serum creatinine was over 2.0 mg/dl, and 24-h urine creatinine clearance less than 60 ml/min. Leukopenia was defined as a white blood count of fewer than 3000 cells per mm^3 and thrombocytopenia, as a platelet count of fewer than 100000 cells per mm^3.

Results

In all, 96 patients were non-randomly selected to receive CAP and 8 patients, to receive CAF. All these patients were evaluated for response and drug toxicity. The responses to CAP therapy were: 4 patients with CR (4%); 12 with PR (13%); 7 with MR (7%); 30 with SD (31%); and 43 with PD (45%). The responses to CAF therapy were: one patient with PR (13%) and 7 with PD (88%) (Table 3). The difference between the response rates to CAP (17%) and to CAF (13%) was not statistically significant (chi-square test). The median duration of survival is 29 weeks with CAP and 22 weeks with CAF (difference not statistically significant according to the generalized Wilcoxon test (Fig. 1). The median duration of survival with CAP therapy was 45 weeks among objective responders (CR + PR), 39 weeks among patients with MR or SD, and 19 weeks for those with PD. There was a statistically significant difference between responders plus stable disease patients and those with progressive disease in the duration of survival (Fig. 2). The median duration of response with CAP therapy was 16.1 weeks (range 4–74 weeks) in the 16 patients in whom objective response was achieved. The influence of prior radiotherapy, surgery, and chemotherapy on the response rate of CAP therapy is illustrated in Table 4. Of the 16 patients who achieved objective response, 4 had undergone prior surgery only, 4, surgery and chemotherapy; 1, surgery and radiation, 3, surgery, chemotherapy and radiotherapy; 1 chemotherapy only; 3 had had no prior treatment. The objective response rates in primary cases and recurrent cases were 14% and 19%, respectively, for CAP therapy. The difference between the two groups was not statistically significant. Remission occurred in regional or peripheral lymph nodes (32%), lung tumors (24%), bladder tumors (14%) and liver tumors (57%). There was no objective response in bone metastasis, pelvic or retroperitoneal local extensions, or adrenal and cutaneous metastases. The median number of courses of CAP therapy was 2.7 (range 1–7). A mean of 3.1 courses of CAP therapy (range 1–5) was delivered to patients who achieved objective response. Various doses of chemotherapeutic agents were administered. In the dose groups receiving less than 29 mg/m^2, 30–39 mg/m^2, 40–49 mg/m^2 and more than

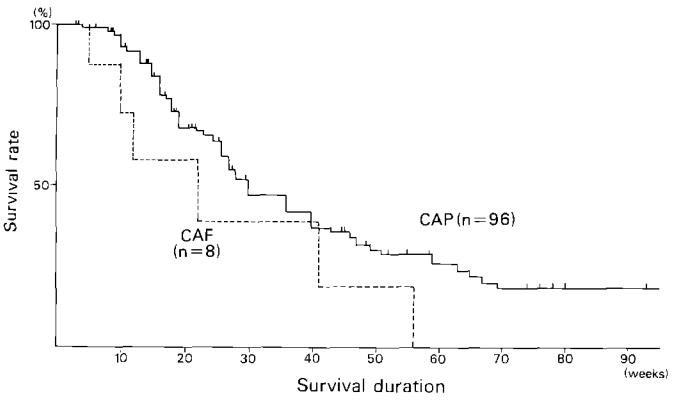

Fig. 1. Survival rate (CAP vs CAF)

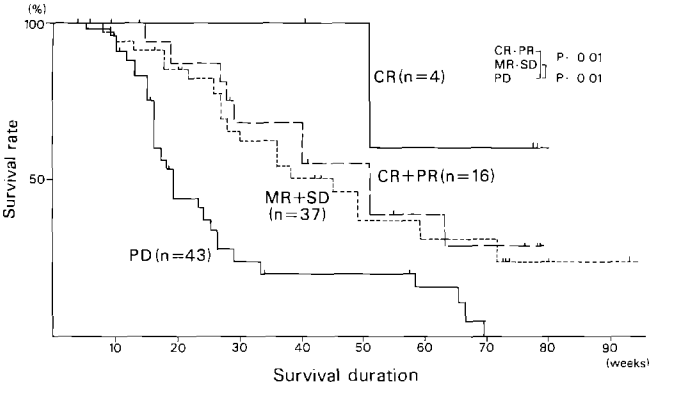

Fig. 2. Survival rate with CAP (CR + PR, MR + SD, PD)

Table 3. Overall response rate to combination chemotherapy

Response	CAP No. (%)	CAF No. (%)	Total No. (%)
CR	4 (4)	0	4 (4)
PR	12 (13)	1 (13)	13 (13)
MR	7 (7)	0	7 (7)
Stable disease	30 (31)	0	30 (29)
Progressive disease	43 (45)	7 (88)	50 (48)
CR + PR/total	16/96 (17)*	1/8 (13)*	17/104 (16)

* Not significant (x^2-test)

Table 4. Influence of previous therapy on response to CAP therapy

Previous therapy	No. of patients	Response		
		CR + PR No. (%)	MR + SD No. (%)	PD No. (%)
Surgery	81	2 + 10 (15)	6 + 29 (43)	34 (42)
Chemotherapy	41	1 + 7 (19)	2 + 15 (42)	17 (42)
Radiotherapy	28	1 + 3 (14)	2 + 8 (36)	14 (50)
No treatment	13	2 + 1 (23)	1 + 1 (15)	8 (62)
S only	32	1 + 3 (13)	3 + 12 (47)	13 (41)
S and R	9	1 (11)	1 + 2 (33)	5 (56)
S and C	22	4 (18)	1 + 9 (45)	8 (36)
S, R and C	18	1 + 2 (17)	1 + 6 (39)	8 (44)
R and C	1			1 (100)
C only	1	1 (100)		

S, surgery; R, radiotherapy; C, chemotherapy

Table 5. Incidence of overall toxicity

Toxicity	CAP (n = 96) No. (%)	CAF (n = 8) No. (%)
Anorexia	86 (90)	4 (50)
Nausea/vomiting	78 (81)	3 (38)
Leukopenia	69 (72)	3 (38)
Fatigue	66 (69)	1 (13)
Anemia	46 (48)	3 (38)
Fever	31 (32)	1 (13)
Alopecia	22 (23)	3 (38)
Diarrhea	19 (20)	–
Renal	16 (17)	3 (38)
Thrombocytopenia	12 (13)	–
Hepatic	8 (8)	1 (13)
Hearing loss	3 (3)	–
Hematuria	3 (3)	–
Cardiovascular	2 (2)	–

50 mg/m^2 the response rates to the initial course of adriamycin were 9%, 21%, 20% and 25%, and those to the initial course of cisplatin were 7%, 19%, 9% and 24%, respectively. All patients achieving CR in response to cisplatin were treated with more than 50 mg/m^2. The overall toxic side effects of treatment in both groups are shown in Table 5. No patient died of these complications of combined chemotherapy. The most common toxicities were anorexia, nausea and vomiting, alopecia, and bone marrow suppression. Renal toxicity occurred in 19 patients (18%), and mild cardiovascular toxicity occurred in 2 patients (2%) but needed no special management. Clinical hearing loss occurred in 3 patients (3%) and hematuria in 3 patients (3%) in the CAP therapy group. Leukopenia was noted in 72 (69%), anemia in 49 (47%) and thrombocytopenia in 12 (13%).

Discussion

Many chemotherapeutic drugs have been tested for palliative treatment, although combined chemotherapy trials in advanced and/or metastatic bladder carcinoma have so far produced only temporary benefits [9]. The response rates to chemotherapeutic agents vary from one institution to another. Published rates of response to the most common non-cisplatin combination, CAF, the response rate range from 0 to 18% [11, 14, 22]. On the other hand, for the most common cisplatin combination, CAP, the response rates given vary from 13% to 83% [1, 2, 10, 11, 16, 21, 25, 27]. Our study was a multi-institutional non-randomized trial comparing the combinations CAP and CAF in patients with advanced and/or metastatic transitional cell carcinoma of the urinary bladder. Of 104 patients, 96 received CAP and 8 received CAF. Some bias seems to have been present in selection of the CAP and CAF arms. In our study, the response to CAF therapy was 13% and that to CAP therapy was 17%. Although the response rate was low, CR was seen in 4 cases (4%), whereas in several other trials the CR rates varied from 0 to 22% (Table 6). Recently, Sternberg et al. combined the two most active combinations, methotrexate + vinblastine and cisplatin + adriamycin, were combined to give a four-drug regimen (M-VAC) in the hope of increasing the CR rate and in fact obtained a CR of 50% [26].

Table 6. Complete and partial responses to CAP therapy in a variety of studies

Complete response No. (%)	Number of CR + PR/Total (%)	Reference
1 (8)	10/12 (83)	[25]
5 (22)	19/23 (82)	[10]
0 (0)	2/15 (13)	[2]
3 (9)	13/34 (38)	[27]
5 (12)	17/42 (40)	[16]
2 (7)	13/28 (46)	[21]
1 (7)	5/14 (36)	[11]
3 (13)	10/23 (43)	[1]
4 (4)	16/96 (17)	Present study
19 (50)	26/38 (68)	[13][a]
12 (50)	17/24 (71)	[26][b]

Values = No. of patients (%)
[a] CAP (i.v. and i.a.)
[b] M-VAC

Other authors report that responders to CAP therapy live significantly longer than non-responders [21, 27]. In our study, the duration of survival in responders and patients with SD was significantly different from that in those with PD.

The response rates obtained with investigational agents in patients with urothelial cancers, especially those previously treated with systemic chemotherapy, have been poor [1]. However, our objective response rate was not influenced by the mode of previous therapy. Patients pretreated with chemotherapy achieved objective response in 19% of cases.

Logothetis et al. [12, 13] reported that patients with locally advanced transitional cell carcinoma of the urothelium or metastatic cases to lymph nodes can benefit from i.v. and i.a. CAP therapy. Various sites of metastasis showed CR or PR. However, in our study there was no objective response in bone metastasis. Thus, if patients with bone metastasis (26 patients) were excluded, the objective response rate would be increased to 23%.

Various doses of adriamycin and cisplatin were given in this study. CR and PR did not differ with various dosages up to 50 mg/m^2, but all cases of CR in the CAP arm were seen with the highest dose of cisplatin (more than 50 mg/m^2). The lower response rate in our study may be due to the lower dosages than in other studies [11, 26].

Combination chemotherapy was relatively well tolerated in all patients, and there were no iatrogenic fatalities. Anorexia, nausea, vomiting or bone marrow suppression were seen in almost all patients (72%–90%). Renal toxicity occurred in 19 patients (18%) and cardiovascular toxicity in 2 patients (2%), but these needed no special management. However, the cardiovascular toxicity of adriamycin and the renal toxicity of cisplatin are well known. Citrin et al. reported that methotrexate combined with CAP therapy makes it possible to reduce the dose of each of the three drugs, and thus lowering the toxicity, without significant loss of efficacy [4].

The results of our study suggest that response to CAP therapy is influenced by patient selection, dosage of cisplatin, and sites of advanced and/or metastatic lesions. We surmise that careful selection of patients, adequate

doses, and suitable methods of administration would result in a higher objective response rate and a longer duration of response.

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