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Combination chemotherapy for advanced urothelial-tract carcinoma*

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Summary. Between December 1982 and November 1990, 31 patients with advanced urothelial carcinoma were treated with one of two combination chemotherapy regimens. A total of 20 patients were treated with 3 mg/m^2 mitomycin C and 300 mg/m^2 cyclophosphamide given intravenously every 10–14 days and with 180 mg/m^2 5-fluorouracil (5-FU) given intravenously every day for as long as possible (CF-Mito regimen). After the patient had been discharged from the hospital, the same treatment with CF-Mito was performed except that 180 mg/m^2 5-FU was replaced by 400 mg/m^2 UFT (a mixture of tegafur and uracil) given orally. A total of 11 patients whose tumor had relapsed during the first-line treatment were given 60 mg/m^2 cisplatin, 40 mg/m^2 Adriamycin, and 40 mg/m^2 methotrexate intravenously every 28 days (PAM regimen). In all, 20 patients received 4–44 (mean, 9.7) courses of CF-Mito over a period of 1.5–24 (mean, 5.3) months. The results obtained in these 20 patients with evaluable lesions included no complete remission (CR), 4 partial remissions (PRs), 9 cases of stable disease (SD), and 7 cases of progressive disease (PD). The PR duration was 1.5–22 (mean, 7.5) months. The side effects encountered in this group included anorexia, nausea, vomiting, myelosuppression, diarrhea, stomatitis, liver damage, and heart failure. In all, 11 patients received 3–7 (mean, 4.1) courses of PAM over a period of 3–14.5 (mean, 5.2) months. All 11 patients had evaluable lesions, and their responses included no CR, 5 PRs, 3 cases of SD, and 3 cases of PD. The PR duration was 1–3 (mean, 1.6) months. The side effects encountered in this group included anorexia, nausea, vomiting, myelosuppression, heart failure, and hair loss.

Introduction

Transitional-cell carcinoma of the urothelial tract is a chemotherapeutically responsive tumor. In recent years, some effective combinations have been reported [4, 11, 12]. However, few effective combination chemotherapy regimens were available in the early 1980s. Between December 1982 and November 1990, two prospective trials involving combinations of three agents were performed to evaluate their efficacy in the treatment of urothelial carcinomas. The first trial tested a regimen consisting of cyclophosphamide, 5-fluorouracil (5-FU), and mitomycin C (CF-Mito regimen), which was applicable even to outpatients without lowering their quality of life [7]. In the second trial [6], the regimen consisted of cisplatin, Adriamycin, and methotrexate (PAM regimen). The latter regimen was developed for patients who had relapsed during treatment with the CF-Mito regimen. The results are presented, and the efficacy of these two regimens is discussed.

Patients and methods

In all, 20 patients were entered in the first trial and 11 were entered in the second trial. All patients had histologically proven transitional-cell carcinoma of the urothelial tract and bidimensionally measurable lesions. The first 20 patients were treated with the CF-Mito regimen between December 1982 and November 1990. This group consisted of 16 men and 4 women, and their average age was 62 years (range, 43–77 years). The primary lesion was located in the bladder in 11 patients and in the renal pelvis and/or ureter in 9 subjects. All 20 patients had undergone surgery for removal of the primary lesion, and 4 subjects (20%) had a history of prior chemotherapy.

The 11 patients in the second trial were treated with the PAM regimen between March 1984 and November 1990. This group consisted of 9 men and 2 women whose mean age was 60 years (range, 42–73 years). The primary lesion was located in the bladder in 7 patients and in the renal pelvis and/or ureter in 4. All 11 patients had undergone surgery for removal of the primary lesion and had a history of prior chemotherapy with the CF-Mito regimen.

All patients had distant metastases, e.g., in the lung, liver, or lymph nodes, and/or local disease. The detailed characteristics of the patients included in each trial are presented in Tables 1 and 2.

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Table 1. Characteristics of patients in the group receiving the CF-Mito regimen

Patient	Age (years)	Sex	Primary lesion	Histology	Prior surgery	Prior chemotherapy	Evaluable lesion	Duration of treatment (months)	Number of courses	Response	Duration (months)	Outcome (months)
A. Y.	72	F	Bladder	TCC	Radical	PPA, 2[a]	Lung, lymph node	3	6	SD	3	Dead (3.5)
S. A.	66	M	Renal pelvis	TCC	Radical	PPA, 2[a]; VP16	Lung, lymph node	1.5	6	PD	(–)	Dead (2)
K. H.	57	M	Renal pelvis	TCC	Radical	PPA, 1[a]; VP16	Lung	8	10	SD	5	Dead (15.5)
Y. T.	51	M	Bladder	TCC	Radical	(–)	Local recurrence	5	11	PR	1.5	Dead (7)
T. T.	67	M	Bladder	TCC	Radical	(–)	Local recurrence	3	4	SD	3	Dead (5)
N. I.	68	M	Bladder	TCC	Palliative	(–)	Lymph node	2	7	PR	1.5	Dead (5)
S. O.	75	M	Bladder	TCC	Radical	(–)	Lymph node	24	44	PR	22	Dead (32) pneumonia
T. H.	58	M	Renal pelvis Ureter	TCC	Radical	(–)	Subcutaneous mass	2	6	PD	(–)	Dead (26)
I. S.	59	F	Renal pelvis Ureter	TCC	Radical	(–)	Bone	4	7	PD	(–)	Dead (10)
R. T.	70	F	Bladder	TCC	Radical	(–)	Local recurrence	3.5	4	PD	(–)	Dead (5.5)
J. S.	72	M	Bladder	TCC	Palliative	(–)	Lymph node	6	13	PR	5	Dead (11)
S. K.	52	M	Renal pelvis	TCC	Radical	(–)	Lymph node	7	14	SD	7	Dead (36.5)
K. K.	51	M	Renal pelvis	TCC	Palliative	(–)	Lung	2	5	PD	(–)	Dead (5)
S. O.	66	M	Bladder	TCC	Radical	(–)	Local recurrence Lymph node	5	12	SD	3.5	Dead (11)
A. M.	77	M	Bladder	TCC	Palliative	(–)	Lymph node	4	11	SD	3	Dead (5)
Y. I.	63	M	Ureter	TCC	Radical	(–)	Bone	11	11	SD	11	Alive (27)
Y. I.	43	M	Bladder	TCC	Palliative	CDDP	Liver	2	5	PD	(–)	Dead (5)
K. O.	47	M	Bladder	TCC	Radical	(–)	Lung	2	5	SD	4	Alive (5)
F. Y.	68	F	Ureter	TCC	Palliative	(–)	Local Mass	5.5	8	PD	(–)	Dead (7)
K. S.	58	M	Ureter	TCC	Radical	(–)	Lymph node	9	6	SD	6	Dead (11)

[a] Number of months; TCC, transitional-cell carcinoma; PPA, cisplatin + peplomycin + Adriamycin; VP16, etoposide; CDDP, cisplatin

Table 2. Characteristics of patients in the group receiving the PAM regimen

Patient	Age (years)	Sex	Primary lesion	Histology	Prior surgery	Prior chemotherapy	Evaluable lesion	Duration of treatment (months)	Number of courses	Response	Duration (months)	Outcome (months)
Y. T.	51	M	Bladder	TCC	Radical	CF-Mito, 11[a]	Local recurrence	3	3	PD	(–)	Dead (3.5)
K. H.	59	M	Renal pelvis	TCC	Radical	PPA, 1[a] CF-Mito, 10[a]	Lung	4	4	SD	4	Dead (7)
S. A.	42	M	Bladder	TCC	Radical	CF-Mito, 4[a] VM26	Lymph node, liver Lung	5	5	PD	(–)	Dead (4)
M. N.	59	M	Bladder	TCC	Radical	CF-Mito, 3[a]	Lymph node	10	7	SD	6	Dead (16)
S. O.	66	M	Bladder	TCC	Radical	CF-Mito, 12[a]	Local recurrence lymph node, lung	14.5	7	PR	3	Dead (17)
T. I.	59	M	Bladder	TCC	Radical	CF-Mito, 10[a]	Lung	3.5	4	PR	1	Dead (3.5)
K. O.	68	F	Bladder	TCC	Radical	CF-Mito, 10[a]	Local recurrence	3	3	SD	3	Dead (5.5)
T. H.	58	M	Renal pelvis Ureter	TCC	Radical	CF-Mito, 6[a]	Subcutaneous mass	3.5	3	PR	2	Dead (23)
S. S.	72	M	Bladder	TCC	Palliative	CF-Mito, 13[a]	Local mass, lung	3	3	PD	(–)	Dead (4)
K. K.	55	F	Ureter	TCC	Radical	CF-Mito, 10[a]	Local recurrence	3	3	PR	1	Dead (7)
N. S.	73	M	Ureter	TCC	Radical	CF-Mito, 10[a]	Lymph node, liver	3	3	PR	1	Dead (5)

[a] Number of courses
TCC, transitional-cell carcinoma; PPA, cisplatin + peplomycin + Adriamycin; VM26, teniposide

CF-Mito regimen. For treatment of inpatients, 3 mg/m^2 mitomycin C and 300 mg/m^2 cyclophosphamide were given intravenously every 10–14 days and 180 mg/m^2 5-FU was given intravenously every day for as long as possible. After the patients had been discharged from the hospital, the same treatment with the CF-Mito regimen was performed except that 5-FU was replaced by 400 mg/m^2 UFT (a mixture of tegafur and uracil) given orally.

PAM regimen. The patients were given 2 l 0.45% saline and 12.5 g mannitol, and were then given 60 mg/m^2 cisplatin intravenously by drip infusion for 1 h. Thereafter, 40 mg/m^2 Adriamycin and 40 mg/m^2 methotrexate were given intravenously by bolus injection on the same day. This course was repeated every 28 days.

Criteria for the evaluation of response. A complete remission (CR) was defined as the disappearance for >1 month of all evidence of disease as assessed by physical examination as well as biochemical, radiographic, and cytologic evaluations. A partial remission (PR) represented a decrease of $\geq$50% in an abnormally elevated parameter directly related to the tumor that lasted for >1 month. Stable disease (SD) defined as a

Table 3. Side effects encountered in the group receiving the CF-Mito regimen

Side effect	Number of patients	Treatment discontinuation[a]
Anorexia, nausea, vomiting	10	–
Myelosuppression	9	4
Diarrhea	3	–
Stomatitis	2	–
Liver damage	1	1
Heart failure	1	1

[a] Number of patients experiencing toxicity requiring the discontinuation of treatment with CF-Mito
Total number of patients who experienced toxicity = 13

Table 4. Side effects encountered in the group receiving the PAM regimen

Side effect	Number of patients	Treatment discontinuation[a]
Anorexia, nausea, vomiting	6	–
Myelosuppression	11	–
Alopecia	6	–
Heart failure	1	–

[a] Number of patients experiencing toxicity requiring the discontinuation of treatment with PAM

change of 40% in all parameters that lasted for at least 3 months. Progressive disease (PD) represented an increase of ≥25% in the size of the tumor or the appearance of new lesions. The duration of the response was measured from the time at which a CR or PR was first achieved.

Results

The 20 patients who participated in the CF-Mito trial received 4–44 (average, 9.7) courses. In all, 4 patients achieved a PR lasting 1.5–22 (average, 7.5) months, and their duration of survival was 5–32 (average, 13.8) months. Of these 4 patients, 1 received 44 courses and showed a PR for 22 months. This patient had undergone cystectomy and developed pelvic-node metastases and local recurrence 1 month later; he was treated on an outpatient basis for 23 months. Another patient had not undergone radical surgery because of respiratory disease; he received 13 courses of CF-Mito over a period of 6 months and showed a PR for 5 months, after which he developed a new lesion. The final 2 patients showed a PR for 1.5 months; 1 had local recurrence and the other had local extension. Both had pelvic-node metastases. A total of 9 patients exhibited SD and 7 others developed PD. The objective response rate (CR+PR) was 20%.

Anorexia, nausea, and vomiting occurred in 10 of the 20 patients (50%); myelosuppression, in 9 (45%); diarrhea, in 3 (15%); stomatitis, in 2 (10%); heart failure, in 1 (5%); and liver damage, in 1 (5%). Of these 13 patients who experienced side effects, 6 were incapable of receiving more than 11, 7, 6, 4, 4, or 4 courses, respectively, because of severe myelosuppression, heart failure, or liver damage (Table 3).

The 11 patients entered in the PAM trial received 3–7 (average, 4.1) courses. In all, 5 patients showed a PR for 1–3 (average, 1.6) months, and the duration of their survival was 3.5–23 (average, 11.1) months. Of these 5 patients, 1 achieved a PR that lasted 3 months. This patient had undergone radical cystectomy and developed local recurrence and lung metastasis 6 years later; he received 7 courses over a period of 14.5 months. Another patient showed a PR for 1 month. This patient had undergone nephroureterectomy; he developed liver and paraaortic node metastases 15 months later and received 3 courses. Yet another patient achieved a PR that lasted 2 months; this patient had undergone nephroureterectomy, developed local recurrence 4 months later, and received 3 PAM courses. The other 2 patients showed a PR for 1 month. A total of 3 patients exhibited SD for 3–6 months (average, 4.3 months), and 2 others developed PD. The objective response rate was 45%.

All 11 patients developed myelosuppression, which did not require any special supporting therapy, and 6 (55%) experienced anorexia, nausea, and vomiting. Hair loss occurred in 6 (55%) cases and heart failure, in 1 (9%; Table 4). The PAM therapy was well tolerated by all 11 patients.

Discussion

Transitional-cell carcinoma (TCC) of the urothelial tract has been considered to be a chemotherapeutically responsive tumor. However, in the early 1980s, few effective regimens had beneficial effects on the survival of patients with advanced urothelial cancer [8–10]. Accordingly, we designed programs for the chemotherapy of patients with advanced disease.

Our first chemotherapeutic program for patients with advanced urothelial carcinoma involved two different protocols: the PPA regimen, which consisted of cisplatin, Adriamycin, and peplomycin, was used as of April 1981; and the CF-Mito regimen was applied as of December 1982 [6]. The patients had been treated mainly with the PPA regimen and were then given the CF-Mito regimen when further treatment became necessary.

Since the PPA regimen had shown no definitive advantage for the treatment of patients with advanced urothelial carcinoma, in December 1983 we designed a third protocol: the PAM regimen, which consisted of cisplatin, Adriamycin, and methotrexate. The CF-Mito regimen, which did not contain cisplatin, was used as first-line chemotherapy, and the PAM regimen was implemented as second-line treatment.

The first-line (CF-Mito) regimen was a combination of cyclophosphamide, 5-FU, and mitomycin C. It yielded a response rate of only 20%, with the mean duration of response being 5.3 months. The mean survival of the partial responders was 13.8 months. Although these results are similar to those reported for other non-cisplatin-containing regimens [1, 5, 10, 14], they are far worse than those obtained using cisplatin-containing regimens [2–4,

8, 9, 11–13]. In our CF-Mito series, one patient showed a PR for 22 months. This regimen caused only a few mild side effects and was applicable even to outpatients. This indicates that the CF-Mito regimen might yield a beneficial effect in selected patients without causing severe side effects.

The PAM regimen, consisting of cisplatin, Adriamycin and methotrexate, was used as second-line chemotherapy. All 11 patients who were treated with the PAM regimen had previously undergone chemotherapy with the CF-Mito regimen and had exhibited SD or developed PD on the latter regimen. The response rate obtained using the PAM regimen was 45%, but no CR was achieved. Five patients achieved a PR that lasted for a mean of 1.6 months, and they survived for a mean of 11.1 months. The results of our PAM series were similar to those previously obtained using cisplatin and Adriamycin in the presence or absence of cyclophosphamide (CAP, CISCA) [8, 9, 13].

However, in the late 1980s, two trials yielded a higher response rate and a longer survival for responding patients. Mayers et al. [4] obtained 14 (28%) CRs and 14 (28%) PRs in 50 adequately treated patients given the CMV regimen, which consisted of cisplatin, methotrexate, and vinblastine. The median survival was 44 weeks for the complete responders and 29 weeks for the partial responders. Sternberg et al. [12] obtained 58 (69%) CRs and PRs in 83 adequately treated patients receiving a combination of cisplatin, methotrexate, vinblastine, and doxorubicin (M-VAC regimen). The median survival was 138 weeks for the complete responders and 48 weeks for the partial responders. The results of these two trials were slightly superior to those obtained in the present series.

The difference between these trials and ours involved the CR rate. In our series, none of the patients achieved a CR as compared with 14 CRs (28%) in the CMV series and 31 CRs (37%) in the M-VAC series. This discrepancy might have been attributable to the following factors:

1. All of the patients in our series had previously received chemotherapy.

2. Our regimen used a slightly lower dose of cisplatin (60 mg/m^2 vs 70 mg/m^2).

3. Our regimen did not include vinblastine (unlike both the CMV regimen and the M-VAC regimen).

4. Our regimen included Adriamycin instead of vinblastine (unlike the CMV regimen).

Nonetheless, the PAM regimen caused fewer side effects than did either the M-VAC regimen or the CMV regimen. Since the response rate is usually lower in patients with a history of prior chemotherapy, the rate of response to our PAM regimen might have been better in patients who had not undergone prior chemotherapy. Therefore, further study is necessary to confirm the efficacy of the PAM regimen in patients with advanced urothelial cancer.

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