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Three-drug combination chemotherapy for advanced urothelial tract carcinoma

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Summary. A prospective chemotherapeutic trial using combinations of three drugs consisting of three different protocols was performed in 24 patients with advanced transitional-cell carcinoma of the urothelial tract between April 1981 and August 1986. All patients had histologically proven transitional-cell carcinoma and bidimensionally measurable lesions. The protocol I (PPA) was a 5-day course of treatment with 20 mg/m^2 cis-platinum and 5 mg/m^2 peplomycin (a derivative of bleomycin) on days 1–5, and 25 mg/m^2 adriamycin on day 1. Protocol II (CFMit) was a 10-day course with 3 mg/m^2 mitomycin-C and 300 mg/m^2 cyclophosphamide on day 1, and 180 mg/m^2 5-fluorouracil on days 1–10. Protocol III (PAM) was a 1-day course comprising 60 mg/m^2 cis-platinum, 30 mg/m^2 adriamycin, and 40 mg/m^2 methotrexate. In protocols I and III, the drugs were administered every 4–5 weeks, while in protocol II, the drugs were administered continuously without any interval. Of the 9 patients who received 1 to 5 PPA courses, only 3 patients showed a minor response. In the 10 patients who received 4 to 44 CFMit courses, 3 (33%) achieved partial remission for 1.5–22 months, and 3 had a minor response. Of the 5 patients receiving 3 to 7 PAM courses, 1 patient achieved partial remission for 5 months, and 1 had a minor response. Myelosuppression, nausea, vomiting, and anorexia were frequently observed in each protocol. Loss of hair was often observed in protocols I and III. Stomatitis and diarrhea were observed in protocol II. Three patients in protocol I, 4 patients in protocol II, and 1 patient in protocol III were unable to tolerate more courses of the regimen due to the severe side effects.

Introduction

Transitional-cell carcinoma of the urothelial tract (i. e., renal pelvis, ureter, bladder, and urethra) is a chemotherapeutically responsive tumor. During the last 10 years, many cytotoxic agents have been used in the treatment of patients with metastatic transitional-cell carcinoma of the urothelial tract. Adriamycin (ADR), cis-platinum (CDDP), cyclophosphamide (CTX), 5-fluorouracil (5FU), and methotrexate (MTX) have proved to be the best of the agents evaluated so far; when applied singly, each of these drugs exhibits definite clinical activities in the treatment of urothelial tract carcinoma [2, 3, 6, 10, 20]. Between April 1981 and August 1986, three prospective trials involving combinations of these three agents were performed to evaluate their efficacy in the treatment of urothelial carcinomas. The first trial employed a regimen consisting of CDDP, peplomycin (PEP; a derivative of bleomycin), and ADR [13]. In the second trial, the regimen consisted of CTX, 5FU, and mitomycin-C (MMC [14]), while in the third trial, the regimen consisted of CDDP, ADR, and MTX. The results are presented, and the efficacy of each regimen is discussed.

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Materials and methods

Materials

Twenty-four patients with histologically proven transitional-cell carcinoma of the urothelial tract and bidimensionally measurable lesions were included in the trials; 20 patients were males, and 4 were females. The average age was 63 years, the range being from 42 to 78 years. Of the 24 patients, 22 had a history of surgery for the removal of the primary lesion. All patients had distant metastases which involved the lungs, liver, bone, and lymph nodes, and/or local recurrence. The characteristics of the patients included in each trial are shown in Table 1.

Methods

Dose schedule

Protocol I: PPA regimen. Nine patients were treated with the PPA regimen (i. e., CDDP, PEP, and ADR) between April 1981 and December 1983 [13]. On day 1, 25 mg/m^2 ADR was administered intravenously by a single bolus injection. On days 1–5, the patients were given 2 L 0.45% saline and 12.5 g mannitol, followed by an intravenous drip infusion of 20 mg/m^2 CDDP for 1 h; 5 mg/m^2 PEP was also given intravenously by a 24-h drip infusion. This course was repeated in 4- to 5-week cycles as long as it could be tolerated by the patients.

Protocol II: CFMit regimen. Ten patients were treated with the CFMit regimen (i. e., CTX, 5FU, and MMC) between December 1982 and August 1986 [14]. On day 1, 300 mg/m^2 CTX and 3 mg/m^2 MMC were administered intravenously by drip infusion. On days 1–10, 180 mg/m^2 5FU was given intravenously by drip infusion. In the case of out-patients, 300 mg/m^2 UFT (a mixture of 5FU and uracil) was

Table 1. Characteristics of the patients in each trial

	Protocol I	Protocol II	Protocol III
Number of patients	9	10	5
Average age (years)	65	64	54
Sex (male/female)	8/1	7/3	5/0
Primary lesion (bladder/pelvis and ureter)	7/2	6/4	3/2
Prior surgery (radical/palliative surgery)	9/0	9/1	4/1
Prior chemotherapy (+/−)	2/7	3/7	4/1
Measurable lesion: lung	2	3	1
liver	2	0	0
lymph node	7	6	3
bone	0	1	0
local	2	4	3

Table 2. Results of protocol I (CDDP, PEP, and ADR)

Response				
	Response	No. of patients	Response rate (%)	Duration of response
	CR	0	0	–
	PR	0	0	–
	MR	3	33	2 months
	SD	3	33	–
	PD	3	33	–
Side effects				
			No. of patients	Frequency (%)
	Anorexia, nausea, vomiting		9	100
	Loss of hair		9	100
	Myelosuppression[a]		7	78
	Renal dysfunction[b]		3	33
	Interstitial pneumonia		1	11

[a] WBC $<4{,}000/\mu l$ and/or platelet count $<100{,}000/\mu l$
[b] Serum creatine >2mg/dl or creatine clearance <20 ml/min

given orally instead of 180 mg/m^2 5FU. This course was repeated without any interval.

Protocol III: PAM regimen. Five patients were treated with the PAM regimen (i. e., CDDP, ADR, and MTX) between March 1984 and August 1986. The patients were given 2 L 0.45% saline and 12.5 g mannitol, and then received 60 mg/m^2 CDDP intravenously by drip infusion for 1 h. Thereafter, 30 mg/m^2 ADR and 40 mg/m^2 MTX were given intravenously by bolus injections on day 1. This course was repeated in 4- to 5-week cycles.

Criteria for the evaluation of response

Complete remission (CR) was taken to mean the disappearance of all evidence of disease as assessed by physical examination as well as biochemically, radiographically, and cytologically for at least 1 month. Partial remission (PR) indicated a 50% or more decrease in the abnormally elevated parameters directly related to the tumor for at least 1 month. Minor response (MR) was a 25%–49% decrease for at least 1 month. Stabilization of disease (SD) was a 25% or less change for at least 3 months. Progression of disease (PD) indicated a 25% or more increase. The duration of the response was measured from the time when CR, PR, and MR had been achieved.

Results

The 9 patients who participated in the PPA trial received 1 to 5 (average, 2.2) courses. No patients achieved CR or PR, so that the objective response rate was 0%. Three patients had MR for 2 months, 3 patients had SD, and 3 patients had PD. Anorexia, nausea and vomiting, and loss of hair were observed in all 9 patients. Myelosuppression (white blood cell count, <4000 per microliter and/or platelet count, $<100{,}000$ per microliter) was observed in 7 patients (78%), renal dysfunction (serum creatinine level, $\geqq 2$ mg/dl, or creatinine clearance, <20 ml/min) was seen in 3 patients (33%), and interstitial pneumonia occurred in 1 patient (11%). Three patients could not tolerate more than 5, 2, or 1 courses, respectively, due to side effects such as interstitial pneumonia, severe myelosuppression, and renal dysfunction (Table 2).

Table 3. Results of protocol II (CTX, 5FU, and MMC)

Response				
	Response	No. of patients	Response rate (%)	Duration of response (months)
	CR	0	0	–
	PR	3	30	1.5–22 (mean, 8.6)
	MR	3	30	1.5– 2.0 (mean, 1.8)
	SD	1	10	–
	PD	3	30	–
Side effects				
			No. of patients	Frequency (%)
	Anorexia, nausea, vomiting		7	70
	Myelosuppression		5	50
	Stomatitis		2	20
	Diarrhea		1	10
	Heart failure		1	10

Table 4. Results of protocol III (CDDP, ADR, and MTX)

Response				
	Response	No. of patients	Response rate (%)	Duration of response (months)
	CR	0	0	–
	PR	1	20	5
	MR	1	20	4
	SD	1	20	10
	PD	2	40	–
Side effects				
			No. of patients	Frequency (%)
	Myelosuppression		5	100
	Nausea and vomiting		5	100
	Loss of hair		3	60

The 10 patients who participated in the CFMit trial received 4 to 44 (average, 10.5) courses. Three patients achieved PR for 1.5–22 (average, 8.6) months. Of these 3 patients, 1 has received 44 courses and has shown PR since November 1984. This patient has pelvic-node metastases and local recurrence. The other 2 patients showed PR for 1.5 months; 1 had local recurrence, the other had local extension, and both had pelvic-node metastases. Three patients had MR for 1.5–2 (average, 1.8) months, 1 patient had SD, and 3 patients had PD. An objective response rate of 30% was observed. Anorexia, nausea, and vomiting were observed in 7 patients (70%). Myelosuppression was observed in 5 patients (50%), stomatitis in 2 patients (20%), diarrhea in 1 patient (10%), and heart failure in 1 patient (10%). Of these 10 patients, 4 could not have more than 7, 6, 4, or 4 courses, respectively, due to severe myelosuppression or heart failure (Table 3).

The 5 patients who participated in the PAM trial received 3 to 7 (average, 4.8) courses. One patient achieved PR for 5 months; this patient had pubic-bone metastasis and received 5 courses. One patient had MR for 4 months, and 1 had SD for 10 months. The other 2 patients had PD. The objective response rate was 20%. All patients had myelosuppression, nausea, vomiting, and anorexia. Loss of hair was observed in 3 patients. Of these 5 patients, 1 was unable to tolerate more than 5 courses due to severe myelosuppression. One patient who achieved PR for 5 months and 1 patient with SD for 10 months received radiotherapy (Table 4).

Discussion

No previous study has demonstrated a definite advantage in performing combination chemotherapy in patients with advanced transitional-cell carcinoma of the urothelial tract, even though a large number of chemotherapeutic trials have been performed. In some studies, the response rates were high, but the duration of the response did not extend beyond 6–9 months [8, 9, 15, 16, 18, 21].

Given this background, we carried out three chemotherapeutic trials using combinations of three drugs in order to evaluate such regimens in the treatment of advanced transitional-cell carcinoma. The regimen consisting of CDDP, PEP (a derivative of bleomycin), and ADR was employed in the first trial [13]. Although previous reports have shown response rates of more than 40% with CDDP-based combinations [4, 7–9, 15, 16, 18, 21, 22], the present regimen, consisting of CDDP, ADR, and PEP failed to produce any objective response. Thus, PEP seems to compromise the effect of CDDP plus ADR against transitional-cell carcinoma. This regimen was abandoned in December 1983.

A regimen consisting of CTX, 5FU, and MMC was employed in the second trial [14]. This regimen was pri-

marily designed for the treatment of out-patients with advanced disease; CDDP was excluded in order to minimize side effects. One-half of the patients could be treated with this regimen without hospitalization, since most of the side effects were easily controlled. The response rate produced by this regimen (30%) was quite good in comparison to the 14%–50% response rate obtained using other combination regimens without CDDP [5, 11, 17, 23]. However, the duration of the response was short, except in the case of 1 patient who achieved PR for 22 months.

In the third trial, MTX was added to a combination of CDDP and ADR. As only 5 patients have so far been treated with this regimen, it is too early to analyze the efficacy of this regimen. In the past few years, MTX has often been employed as an agent for combination chemotherapies in the treatment of advanced transitional-cell carcinoma. As a single agent, MTX has been shown to have a response rate of 38% [20], this rising to 45%–68% when it is used in combination with CDDP [1, 12]. A combination of CDDP, ADR, vinblastine, and MTX has been found to have a response rate of 71% [19]. Such combination chemotherapy could yield a CR for mean period of 9.5 months in 50% of patients. MTX is clearly a valuable agent for the treatment of advanced transitional-cell carcinoma.

We are planning to continue the regimen consisting of CDDP, ADR, and MTX as well as that consisting of CTX, 5FU, and MMC in the treatment of advanced transitional-cell carcinoma.

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