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Treatment of gynecological malignancies with a combination of cisplatin, Adriamycin and ifosfamide*, **

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Summary. Histogenetic similarities in the female genital system suggest that a group of cancers from the coelomic epithelium may have a common sensitivity to cytotoxic treatment. A total of 24 patients with evaluable gynecologic cancer were treated with a new combination regimen consisting of cisplatin (50 mg/m^2), Adriamycin (50 mg/m^2), and ifosfamide (1 g/m^2 × 5 days) (PAI) given in five courses at 4-week intervals. The tumors included ten cervical, four endometrial, seven ovarian, and three peritoneal cancers. In all, 20 of our patients had recurrent disease and had previously received other cytotoxic treatment, including radiation (11 cases), cisplatin-containing chemotherapy (8 cases), or both (1 case). As a schedule modification, PAI plus bleomycin (20 mg/m^2, on days 1 and 8) was recommended for tumors containing squamous components. According to the response criteria of the International Union Against Cancer (UICC), a 96% response rate was obtained (cervical, 9/10; endometrial, 4/4; ovarian, 7/7; peritoneal, 3/3). Of 23 responders 8 (35%) achieved a complete remission. The dose-limiting side effect of the PAI regimen was hematologic toxicity: grade 4 leukopenia was observed in 92% of patients, and grade 4 thrombocytopenia was seen in 17%. However, the myelosuppresion reversed spontaneously within 3 weeks, and none of the patients was incapable of completing the planned treatment courses. The results suggest that PAI combination chemotherapy is effective and can be used in the management of patients with gynecologic malignancies derived from the coelomic epithelium (müllerian tumor group).

Introduction

According to a challenging concept by Lauchlan [5, 6], most gynecologic cancers are categorized as being tumors derived from the primary and secondary müllerian systems. The müllerian duct and the covering epithelium of the ovary are indeed formed from the coelomic epithelium between the lateral and medial coelomic bay during the early embryonic stage. This histogenetic similarity leads us to expect that a group of gynecologic tumors may have a common chemosensitivity.

A combination of cisplatin, Adriamycin, and cyclophosphamide (PAC) is now widely accepted as useful in treating ovarian cancer [11] and, more recently, endometrial carcinoma [12]. Since the therapeutic synergism of ifosfamide and cisplatin had been indicated in an experimental investigation [13], cyclophosphamide in the PAC regimen was replaced by ifosfamide at National Kokura Hospital in 1985. The purpose of this paper is to document the therapeutic results of a modified PAC regimen consisting of cisplatin, Adriamycin, and ifosfamide (PAI) in evaluable cancers derived from the extended müllerian system.

Patients and methods

For this study 24 women aged 35–76 years (median, 59.7 years) with measurable gynecologic cancer were selected from 74 patients who had received the same combination chemotherapy at our institution from 1985 to 1988. The patients' characteristics are summarized in Table 1. All patients were staged according to International Federation of Gynecology and Obstetrics (FIGO) criteria [9] and by postsurgical TNM classification [4] at the first operation. As shown in the table, 19 of 24 patients had progressive cancer of FIGO stage III or more. A total of 12 cases, including 10 cervical cancers, 1 endometrial and 1 ovarian cancer, had previously been treated with radiation, and 5 patients with cervical cancer had also simultaneously received hydroxyurea as a radiation potentiator [10]; 8 patients had undergone PAC combination therapy. Because of disease recurrence in the abdominal cavity after a negative second-look operation following five courses of PAI treatment, one patient (case 12) with recurrent endometrial cancer was also included in this study.

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Table 1. Profile of 24 patients with evaluable gynecologic cancer from the extended müllerian system

Case	Age	Primary site	Stage: FIGO (pTNM)		Hystology	Prior treatment	Site of measurable lesion	Addendum
1.	54	Cervix	Ib	pT1N1M0	SCC, NKL	RH, rad.	pelvis, vagina	recurrent
2.	55	Cervix	IIa	pT2N1M0	SCC, NKL	RH, rad.	pelvis, vagina	recurrent
3.	36	Cervix	IIa	pT2N1M0	argyro.	RH, rad., HU	lung, vagina	recurrent
4.	39	Cervix	IIb	pT2N1M0	SCC, NKL	RH, rad.	subCN., AorN.	recurrent
5.	35	cervix	IIb	pT2N1M0	adenosq.	RH, rad., HU	pelvis	recurrent
6.	54	Cervix	IIIb		endomet.	rad., HU	pelvis	recurrent
7.	58	Cervix	IIIb		adenosq.	rad., HU	SubCN.	recurrent
8.	71	Cervix	IIIb	pT3NxMx	SCC, Kera.	ex.lapa., rad.	subCN., pelvis	recurrent
9.	58	Cervix	IIIb	pT3N1M0	SCC, Kera.	TAH, BSO, PLD, rad., HU	pelvis	recurrent
10.	72	Cervix	IIIb		SCC, Kera	rad.	pelvis, cervix	recurrent
11.	62	Corpus	III	pT4N4M1	endomet.	TAH, BSO, PLD, OMT	abdomen	
12.	52	Corpus	III	pT4N1M0	undif.	TAH, BSO, OMT, PAI5	abdomen	recurrent
13.	64	Corpus	III	pT2N0M0	endomet.	RH, OMT, PAC5	lung	recurrent
14.	72	Corpus	IV	pT4NxMx	serous	ex.lapa., PAC3, rad.[a]	pelvis	recurrent
15.	52	Ovary	IIc	pT2NxMx	serous	TAH, BSO, OMT, PAC5	abdomen	recurrent
16.	43	Ovary	IIIc	pT3NxMx	mucinous	ex.lapa., PAC5	abdomen	recurrent
17.	56	Ovary	IIIb	pT3NxMx	serous	BSO, OMT, PAC5	abdomen	recurrent
18.	69	Ovary	IIIc	pT3NxMx	mucinous	ex.lapa., PAC3	abdomen	recurrent
19.	70	Ovary	IIIc	pT3NxMx	serous	TAH, BSO, OMT, rad.	abdomen, pelvis	recurrent
20.	70	Ovary	IV	pT4NxM1	serous	ex.lapa.	lung, abdomen	
21.	68	Ovary	IIIa	pT3NxMx	serous	TAH, BSO, OMT, PAC5	lung, abdomen	recurrent
22.	72	Peritoneum			serous	TAH, BSO, OMT, PAC5	abdomen	recurrent
23.	75	Peritoneum			mucinous	TAH, BSO, OMT, App.	abdomen	
24.	76	Peritoneum			SCC, Kera.	Ex.lapa.	abdomen	

SCC, squamous-cell carcinoma; NKL, large-cell nonkeratinizing; Kera, keratinizing; argyro., argyrophil-cell carcinoma; adenosq., adenosquamous carcinoma; endomet., endometrioid adenocarcinoma; undif., undifferentiated carcinoma; RH, radical hysterectomy; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLD, pelvic lymph node dissection; OMT, omentectomy (partial); ex.lapa., exploratory laparotomy; App., appendectomy; rad., radiation; HU, hydroxyurea; AorN., periaortic lymph node; subCN., subclavicular lymph node; PAC5, 5 courses of cisplatin, Adriamycin, and cyclophosphamide

[a] This patient had received radiation therapy for cervical cancer 11 years before

Table 2. Schedule of PAI (PAI plus B) combination therapy[a]

	Day 1	Day 2	Day 3	Day 4	Day 5
50 mg/m^2 cisplatin	+				
50 mg/m^2 Adriamycin	+				
1 g/m^2 ifosfamide	+	+	+	+	+
400 mgx 3 mesna	+	+	+	+	+

[a] PAI plus B: the addition of 20 mg/m^2 bleomycin (on days 1 and 8) to the PAI regimen

The regimen PAI consists of 50 mg/m^2 cisplatin and 50 mg/m^2 Adriamycin, both given on day 1, and 1 g/m^2 ifosfamide infused daily for 5 days. As a schedule modification, 20 mg/m^2 bleomycin given on days 1 and 8 was added to the PAI combination (PAI plus B) for cancers containing squamous components. The treatment schedule for PAI (PAI plus B) combination therapy is given in Table 2. At least five courses of PAI treatment were recommended at 3- to 4-week intervals. To prevent ifosfamide-induced hemorrhagic cystitis, 400 mg/m^2 2-mercaptoethane sulfonate (mesna) (kindly supplied by Shionogi & Co., Ltd) was given at 0, 4, and 8 h following the ifosfamide infusion.

Responses and toxicities were evaluated according to the criteria recommended by the International Union Against Cancer (UICC) [8]. In addition to routine hematologic and biochemical examinations, which were repeated before every treatment course, abdominal computerized tomography or ultrasonography was carried out where clinically indicated. In cases in which severe bone marrow suppression (grade 4) developed and could not be reversed within 3 weeks, the Adriamycin dose was reduced by 25% for subsequent courses. Patient survival was determined from the 1st day of PAI combination therapy.

Results

Responses to PAI treatment of patients with uterine, ovarian, or peritoneal tumors are shown in Tables 3 and 4. The total response rate was 96% (23/24 cases), including 8 complete responses (CRs) and 15 partial responses (PRs). The median progression-free interval was 7.2 months (range, 3–19 months). The median survival from the initiation of PAI treatment was 11.8 months (range, 6–23 months). The median survival of PR cases was 10.2 months, whereas that of CR cases was 15.3 months; the CR cases included four patients who still show no evidence of disease (cases 1, 11, 20, 23).

Of 12 previously irradiated patients, 11 (92%) obtained clinical remissions, with 3 CRs (27%). Nine cases with recurrence in the radiation field also responded to this therapy. All patients who had received prior PAC chemotherapy also achieved clinical remissions for a 100% response rate (7 PRs and 1 CR) and a median duration of 6.4 months. The only tumor that did not regress was an argyrophil-cell carcinoma of the uterine cervix, which rapidly progressed during the sixth course of PAI treatment, and the patient's condition continued to deteriorate despite changes in the regimen.

The dose-limiting toxicity of this therapy was hematologic: 22 patients (92%) experienced grade 4 leukopenia

Table 3. Responses of uterine and cervical cancers to PAI treatment

Primary tumor	Case	Courses (*n*)	Response	Duration (months):	
				Remission	Survival
Cervical cancer	1 (r)	5	CR	18	20[a]
	2 (r)	5	PR	4	10
	3 (r)	6	NC	4	9
	4 (r)	5	CR	6	13
	5 (r)	5	PR	4	11
	6 (r)	5	PR	3.5	9
	7 (r)	5	CR	6	10
	8 (r)	5	PR	5	11
	9 (r)	5	PR	4	10
	10 (r)	5	PR	3	9
Endometrial cancer	11	5	CR	19	23[a]
	12 (p)	8 (5+3)[b]	PR[b]	5[b]	19
	13 (p)	6	CR	8	12[a]
	14 (r, p)	5	PR	6	8

[a] Still alive

[b] Response and duration for additional PAI treatment following a negative second-look operation

CR, complete response; PR, partial response; NC, no change; (p), previously received cisplatin containing chemotherapy; (r); previously received radiation therapy

Table 4. Response of extrauterine cancers to PAI treatment

Primary tumor	Case	Courses (*n*)	Response	Duration (months):	
				Remission	Survival
Ovarian cancer	15 (p)	5	PR	7	12[a]
	16 (p)	5	PR	6	8
	17 (p)	6	PR	8	10[a]
	18 (p)	5	PR	6	8
	19 (r)	5	PR	6	9
	20	6	CR	11	14[a]
	21 (p)	5	PR	5	8
Peritoneal cancer	22 (p)	6	PR	4	11
	23	5	CR	13	16[a]
	24	5	CR	12	14[a]

[a] Still alive

Table 5. Toxic effects of PAI (PAI plus B) treatment in 24 patients

Toxic effects	Number of patients
Alopecia (grade 2)	24 (100%)
Nausea (grade 1–2)	24 (100%)
Leukopenia (grade 4)	22 (92%)
Vomiting (grade 2)	12 (50%)
Thrombocytopenia (grade 4)	4 (17%)
Muscle pain and spasms (grade 1)	4 (17%)
Mild depression (grade 1)	3 (13%)
Skin pigmentation (grade 1)	2 (8%)
Congestive heart failure (grade 2)	1 (4%)
Microscopic hematuria	1 (4%)
Renal insufficiency	0
Macroscopic hematuria	0

that required intensive antibiotic treatment in an isolated room, and grade 4 thrombocytopenia was observed in 4 patients (17%). Because of prolonged recovery from severe myelosuppression in six patients, their Adriamycin dose had to be reduced for subsequent courses. The use of mesna completely prevented the occurrence of macroscopic hematuria. The other side effects, including cardiac, renal, pulmonary, and CNS toxicities, were not remarkable, although all patients inevitably experienced various degrees of nausea and complete alopecia (Table 5).

Discussion

Considering our patient population, 83% of which were recurrent cases, the results obtained indicate that the PAI combination was powerfully effective in the treatment of gynecologic cancers of various origins and histologies. Even in the patient with argyrophil-cell carcinoma, an intractable cancer of the uterine cervix [1], 4 months of progression-free interval were observed. Although the curative potential of this regimen remains to be proved, the extremely high response rate suggests that malignant tumors from the primary or secondary müllerian system have a similar chemosensitivity to PAI.

We modified the known PAC regimen for two reasons. First, ifosfamide given as a single agent is effective against cervical cancer, and the response rate and survival of patients are comparable with those obtained by cisplatin treatment [7]. Furthermore, from a preliminary result of our previous study [14], we believe that ifosfamide alone is also effective against ovarian cancer. These results indicate the therapeutic utility of ifosfamide in the control of cancers in the müllerian tumor group. The second reason is the reported synergism of ifosfamide and cisplatin [13], even at subtherapeutic doses [2, 3].

In conclusion, PAI combination chemotherapy proved to be effective against several gynecologic cancers. Its severe but controllable toxicity enables this combination to become one of the standard regimens used in the management of patients with gynecologic malignancies in the müllerian tumor group.

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