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Abstract

We evaluated the efficiency and toxicity of estramustine phosphate (ECT), ifosfamide (IFM) and cisplatin (CDDP) combination chemotherapy in twenty-one patients with hormone-refractory prostate cancer (HRPC), for which there is currently no effective treatment. Patients received a daily dose of 560 mg ECT in combination with 1.2 g/m2 IFM on days 1 to 5 and 70 mg/m2 CDDP on day 1. This combination therapy was given every 3 to 4 weeks. An objective response of more than 50% reduction in prostate-specific antigen was observed in 9 of 18 patients (50%), and a more than 50% reduction in bi-dimensionally measurable soft-tissue lesions was observed in 2 of 7 patients (29%). The median duration of response among the cases showing partial response was 40 weeks, while the median duration of response of overall partial-response plus stable cases was 30 weeks. The median survival duration of all cases was 47 weeks. Toxicity was modest and acceptable. In conclusion, the ECT, IFM and CDDP combination chemotherapy regimen is a viable treatment option for HRPC. However, in comparison with our previous chemotherapy regimen of IFM and CDDP, no additional long-lasting effects resulting from the inclusion of ECT could be affirmed.

KEYWORDS: hormone-refractory prostate cancer, chemotherapy, estramustine phosphate, ifosfamide, cisplatin

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Original Article

Combination Chemotherapy with Estramustine Phosphate, Ifosfamide and Cisplatin for Hormone-refractory Prostate Cancer

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We evaluated the efficiency and toxicity of estramustine phosphate (ECT), ifosfamide (IFM) and cisplatin (CDDP) combination chemotherapy in twenty-one patients with hormone-refractory prostate cancer (HRPC), for which there is currently no effective treatment. Patients received a daily dose of 560 mg ECT in combination with 1.2 g/m^2 IFM on days 1 to 5 and 70 mg/m^2 CDDP on day 1. This combination therapy was given every 3 to 4 weeks. An objective response of more than 50% reduction in prostate-specific antigen was observed in 9 of 18 patients (50%), and a more than 50% reduction in bi-dimensionally measurable soft-tissue lesions was observed in 2 of 7 patients (29%). The median duration of response among the cases showing partial response was 40 weeks, while the median duration of response of overall partial-response plus stable cases was 30 weeks. The median survival duration of all cases was 47 weeks. Toxicity was modest and acceptable. In conclusion, the ECT, IFM and CDDP combination chemotherapy regimen is a viable treatment option for HRPC. However, in comparison with our previous chemotherapy regimen of IFM and CDDP, no additional long-lasting effects resulting from the inclusion of ECT could be affirmed.

Key words: hormone-refractory prostate cancer, chemotherapy, estramustine phosphate, ifosfamide, cisplatin

Androgen ablation and secondary hormonal maneuvers are effective in treating metastatic prostate cancer, but there are limited options for the treatment of hormone-refractory disease. To date, chemotherapy has been shown to improve quality of life but not survival in symptomatic patients [1, 2]. There is still no standard treatment for the many patients with hormone-refractory disease and a simultaneous rise in prostate-specific antigen (PSA) or radiological progression. Even though a rise in PSA is a harbinger of clinical metastatic disease, the median survival from development of hormone-refractory disease to death is only several months [3]. In our previous study, which combined ifosfamide (IFM) and cisplatin (CDDP) (IP therapy), IP therapy was shown to have consistent effects, but the necessity of

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devising a more potent chemotherapy with longer-lasting activity was also recognized [4]. According to a study that compared vinblastine (VLB) monotherapy with combined VLB + ECT therapy, ECT appeared useful: time to progression was prolonged and the percentage of cases exhibiting 50% or greater reduction in PSA was significantly higher in the combined therapy group [5]. Based on these findings, we undertook the present study to examine the efficacy and safety of a 3-drug combination chemotherapy (EIP therapy) involving ECT, IFM and CDDP.

Patients and Methods

Patients were considered eligible for this study if they had progressive prostate cancer defined by 2 or more serial increases of PSA values of at least 4 ng/ml obtained at least 2 weeks apart, or progressive radiological disease, following androgen ablation, an antiandrogen, and antiandrogen withdrawal. Patients were also required to meet the following criteria: (1) well-preserved functioning of major organs (Hb > 9.0 g/dl, WBC > 4000/mm^3, GOT and GPT ≤ twice the normal level, total bilirubin < 1.5 mg/dl, serum creatinine < 2.0 mg/dl, and creatinine clearance > 50 ml/min); (2) a performance status (PS) between 0 and 3; (3) age between 20 and 75 years; (4) a survival expectancy of at least 3 months; and (5) provision of written informed consent. Patients were excluded from this study if (1) they had been treated previously with ECT, IFM or CDDP; (2) they had received radiotherapy within 8 weeks before initiation of this study; (3) they had serious complications; or (4) they had active double cancer. The clinical protocol was approved by the Okayama University Hospital Clinical Trials Review Committee, and by the relevant institutional review boards.

EIP therapy was administered according to the following schedules. ECT was orally administered every day at a dose of 560 mg/day; IFM was administered intravenously (1.2 g/m^2) on days 1 through 5; and CDDP was administered intravenously (70 mg/m^2) on day 1. The administrations of IFM and CDDP were repeated for each cycle every 3 weeks. Thereafter, ECT was administered continuously as a maintenance therapy.

The effects of this treatment were evaluated according to the *General Rules for Surgical and Pathological Studies on Prostate Cancer* (3 rd edition) [6]. Survival rate was calculated using the Kaplan-Meier method.

Adverse reactions were reported in accordance with the nomenclature used in the *Criteria for Evaluation of Reinforced Efficacy of Chemotherapy for Solid Cancer*, prepared by the Japan Society of Clinical Oncology.

Results

Background factors (Table 1): Twenty-two patients with hormone-refractory prostate cancer (HRPC) who received treatment at our institution between August 1995 and August 2001 were enrolled in this study. Twenty-one of these patients were included in the final subject group, with 1 patient who received radiotherapy during EIP therapy being excluded. Prior therapies consisted of hormonal therapy (n = 15 patients), chemotherapy (n = 2), radiotherapy for the prostate gland (n = 3), and radiotherapy for the lumbar vertebrae (n = 1).

Table 1 Patient Characteristics — Comparison with IP Chemotherapy —

		IP (n = 27)	EIP (n = 21)
Age (y.o.)		60–77 (Median67)	51–79 (Median66)
Performance status	0	7	8
	1	11	11
	2	6	1
	3	1	1
	4	2	0
Stage	C	2	1
	D1	1	0
	D2	24	20
Grade	well	1	0
	mod	13	8
	por	12	13
Measurable Disease			
Lymph Nodes		7	7
Breast		0	1
Lung		2	0
Prior Therapy			
Hormonal only		7	15
Hormonal + chemotherapy		14	2
Horomonal + radination		6	4

In our previous study, on the other hand, the subject group consisted of 27 patients who received IP therapy for HRPC between January 1990 and May 1995, and only 7 patients had received prior hormonal therapy, while 14 and 6 had received prior chemotherapy or radiotherapy, respectively.

Dose level: EIP therapy was administered for 1 to 4 cycles (median: 3 cycles). Sixteen patients received 2 or more cycles. Five patients received only 1 cycle because of general fatigue and gastrointestinal symptoms (n = 1), renal dysfunction (n = 1), myocardial infarction (n = 1), or severe bone marrow suppression (n = 2).

Response (Table 2): The locations of the lesions were as follows: PSA (n = 18), prostate (n = 16), bone (n = 14), lymph nodes (n = 7) and mammary glands (n = 1). Seventeen cases had more than one location: PSA + bone (n = 10); PSA + lymph nodes (n = 5); PSA + bone + lymph nodes (n = 2); and PSA + bone + mammary glands (n = 1). A 50% or greater decrease in PSA response was recognized in 9 (50%) of the 18 patients. In the measurable lesions, 2 of the 7 patients (29%) with lymph node metastasis and the patient with breast metastasis showed 50% or more reduction. The primary lesion remained stable in 13 (81%) of the 16 patients, whereas 3 patients (19%) showed progression. In addition, evaluation of bone metastasis by bone scintigraphy revealed a marked decrease in radioactivity uptake in 2 of 14 patients.

The overall patient response rate was PR (partial response) in 3 (15%), NC (no change) in 11 (52%, including 7 stable cases), and PD (progressive disease) in 7 (33%) patients. The percentage of PR + stable cases, which is described as an important parameter in the General Rules for Surgical and Pathological Studies on Prostate Cancer, was 33% in this study [6].

In IP therapy, a 50% or greater decrease in PSA response was recognized in 7 (30%) of the 21 patients. In the measurable lesions, 3 of the 7 patients (43%) with lymph node metastasis showed 50% or more reduction, But no response in the patient with lung metastasis. The primary lesion remained stable in 16 (89%) of the 18 patients, whereas 2 patients (11%) showed progression.

In the 3 patients with PR, anti-tumor effects remained for 18 to 90 weeks (median progression-

Table 2 Response Status of EIP Chemotherapy — Comparison with IP Chemotherapy —

2a Response Status of IP Chemotherapy

		CR	PR	NC [ST]	PD
Prostate	(N = 18)	0 (0%)	3 (17%)	13 (72%)	2 (11%)
Bone	(N = 17)	0 (0%)	1 (6%)	14 (82%)	2 (12%)
Lymph node	(N = 7)	1 (14%)	2 (29%)	3 (43%)	1 (14%)
Lung	(N = 2)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
PSA	(N = 21)	4 (19%)	3 (14%)	9 (43%)	5 (24%)
Total	(N = 27)	0 (0%)	7 (26%)	13 (48%) (10 (37%))	7 (26%)

2b Response Status of EIP Chemotherapy

		PR	NC [ST]	PD
Prostate	(N = 16)	0 (0%)	13 (81%)	3 (19%)
Bone	(N = 14)	2 (14%)	9 (65%)	3 (21%)
Lymph node	(N = 7)	2 (29%)	2 (29%)	3 (42%)
Breast	(N = 1)	1 (100%)	0 (0%)	0 (0%)
PSA	(N = 18)	9 (50%)	8 (44%)	1 (6%)
Total	(N = 21)	3 (15%)	11 (52%) (7 (33%))	7 (33%)

PR, partial response; NC, no change; ST, stable disease; PD, progressive disease

free survival period = 40 weeks). On the other hand, in the 7 patients with PR + stable cases, anti-tumor effects remained for 16 to 165 weeks (median progression-free survival period = 30 weeks). For the entire series, the median progression-free survival period was 16 weeks. The 3-year survival rate was 13%, and the median survival duration was 47 weeks (Fig. 1). The median progression-free survival period was 21 weeks. The 3-year survival rate was 36%, and the median survival duration was 92 weeks in IP therapy.

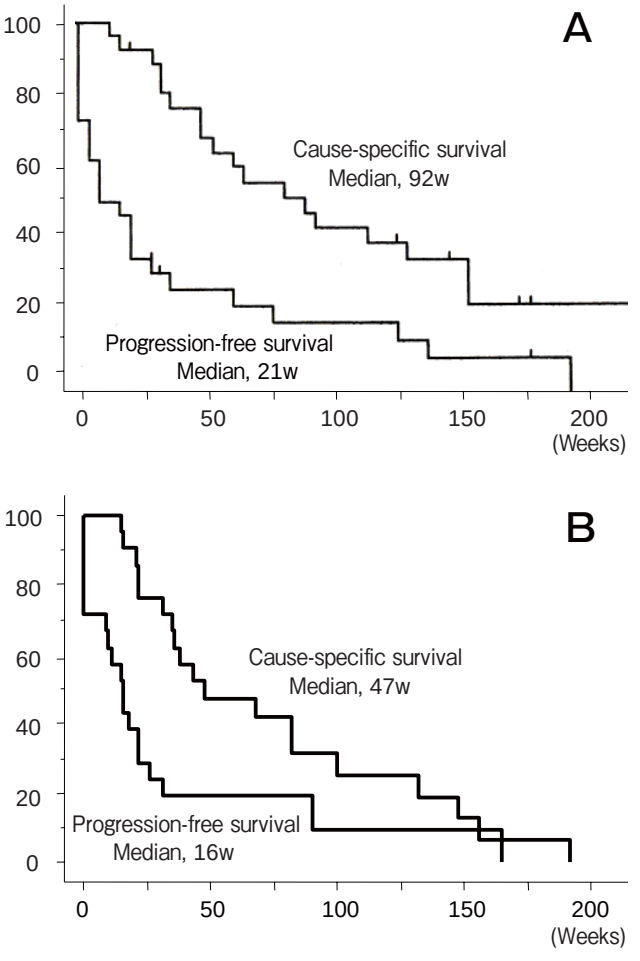

Fig. 1 **A:** Cause-specific survival and progression-free survival of IP. The median progression-free survival period was 21 weeks. The 3-year survival rate was 36%, and the median survival duration was 92 weeks.
B: Cause-specific survival and progression-free survival of EIP. The median progression-free survival period was 16 weeks. The 3-year survival rate was 13%, and the median survival duration was 47 weeks.

The anti-tumor response of EIP therapy was assessed with background factors. When considering histological differentiation of cancer cells, the response was PR in 2, and NC in 4 of the 8 patients with moderaPhoney-differentiated cancer. Of the 13 patients with poorly-differentiated cancer, 1 was PR and 7 were NC (stable cases in 4 patients). Of the 15 patients who had received endocrine therapy alone prior to EIP therapy, 1 PR and 9 NC (3 stable cases) were observed. Of the 6 patients who underwent tegaful-based therapy or radiotherapy, 2 PR and 2 NC (1 stable case) were observed. As for subjective symptoms, there was a decrease in pain and an improvement in voiding disorder in 6 (29%) of the 21 cases. The adverse reactions are shown in Table 3. As subjective adverse reactions, nausea and vomiting were frequently noted (67%). Alopecia was observed in 48% of all patients. Hematologically, bone marrow suppression was frequently noted. Anemia was observed in 16 (76%) of the 21 patients. Among the patients with anemia, 29% were rated as grade 3, and 3 patients required red blood cell transfusions. Leukocytopenia was noted in 12 (57%) of the 21 patients, with the percentage of patients with grade 3 leukocytopenia being 19%. Neutrophil counts were below 500/mm^3 in 2 patients and concomitant G-CSF administrations were required in 4. Thrombocytopenia was noted in 10 (48%) of the 21 patients, and was grade 3 in 14%. Platelet transfusions were required in 2 cases. Biochemically, liver dysfunction was noted in 4 patients (19%), including 2 patients with grade 3 findings, and renal dysfunc-

Table 3 Toxicity of EIP Chemotherapy (n = 21) — Comparison with IP Chemotherapy (n = 27) —

	Incidence (%)		Grade 3 (%)	
	IP	EIP	IP	EIP
Nausea/Vomiting	20 (74%)	14 (67%)	4 (15%)	1 (5%)
Alopecia	18 (67%)	10 (48%)	–	–
Anemia	20 (96%)	16 (76%)	3 (12%)	6 (29%)
Leukocytopenia	24 (89%)	12 (57%)	9 (33%)	4 (19%)
Thrombocytopenia	6 (22%)	10 (48%)	2 (7%)	3 (14%)
Hepatic toxicity	2 (7%)	4 (19%)	0 (0%)	2 (10%)
Renal toxicity	5 (19%)	5 (24%)	1 (4%)	0 (0%)

tion was noted in 5 patients (24%). All of these abnormalities subsided following treatment, except in 1 patient in whom marked liver dysfunction was noted and bone marrow suppression prompted discontinuation of therapy after one cycle. Deep venous thrombosis was observed in 1 patient, and myocardial infarction developed in another.

Discussion

At present, there is no widely accepted method of treatment for hormone-refractory prostate cancer. We previously conducted combined IFM + CDDP chemotherapy (IP therapy) for 27 patients with advanced prostate cancer. In that study, the period of efficacy was short, suggesting the necessity of devising a more potent chemotherapy [4]. In the present study, we attempted EIP therapy, adding ECT to IP therapy. ECT is a drug produced by carbamate binding of estradiol to nitrogen mustard. Because degradation of ECT releases estrogen, keeping the blood testosterone level in the castration range, combined use of LH-RH agonist is unnecessary. The rate of response to ECT therapy is about 90% in untreated fresh cases, but is as low as about 20% in hormone-refractory cases [7]. Attempts have been made to use ECT in combination with one or more of vinblastine, paclitaxel, docetaxel, etoposide, *etc.* [8–19].

In a study that compared ECT + VLB combination therapy with VLB monotherapy in 192 patients [5], the percentage of patients with 50% or greater decrease in PSA was significantly higher in the ECT + VLB group (40%) than in the VLB group (5%). The 50% progression-free survival period was significantly longer in the ECT + VLB group (3.7 months) than in the VLB group (2.1 months) ($p < 0.001$). When adverse reactions were analyzed in that study, the incidences of queasiness and edema were significantly higher in the combined therapy group than in the monotherapy group. The severity of granulocytopenia was significantly lower in the combined therapy group, suggesting that ECT can suppress VLB-induced granulocytopenia.

In the present study, the percentage of patients with 50% or greater decrease in PSA following EIP therapy was 50%, whereas only 33% of patients achieved such a decrease by IP therapy in our previous series. Thus, the concomitant administration of ECT may enhance early response. However, the median progression-free survival period was 40 weeks for the 3 patients with PR to EIP therapy and 30 weeks for the 7 patients with PR + stable cases. Conversely, of the patients treated with IP therapy, the median progression-free survival period was 69 weeks for the 7 with PR and 43 weeks for the 7 with PR + stable cases. There had a complete respone in 1 (14%) with lymph node, 4 (19%) on PSA from the IP therapy, But no one from EIP therapy. The median progression-free survival period and the

Table 4 Estramustine Phosphate (ECT) Based Chemotherapy

Regimen	Author	No. of Pts.	No. (%) with PSA Decrease 50%	No. (%) with CR/PR in Measurable Disease	Median Survival
ECT + vinblastine	Seidman[8]	25	13/24 (54%)	2/5 (40%)	7 months
	Hudes[9]	40	22/36 (61%)	1/7 (14%)	48 weeks
	Hudes[5]	95	35/87 (40%)	6/30 (20%)	48 weeks
ECT + paclitaxel	Hudes[10]	34	17/32 (53%)	4/9 (44%)	69 weeks
	Haas[11]	24	9/24 (37%)	6/13 (46%)	18.9 months
ECT + paclitaxel + etoposide	Smith[12]	40	26/40 (65%)	10/22 (45%)	13 months
ECT + paclitaxel + carboplatin	Kelly[13]	56	40/56 (67%)	19/33 (45%)	19.9 months
ECT + docetaxel	Kreis[14]	17	14/17 (82%)	– (16%)	–
	Petrylak[15]	34	20/32 (63%)	5/18 (28%)	–
ECT + docetaxel + hydrocortisone	Savarese[16]	47	30/44 (68%)	12/24 (50%)	20 months
ECT + etoposide	Pienta[17]	62	24/62 (39%)	8/15 (53%)	56 weeks
	Dimopoulos[18]	56	30/51 (59%)	15/33 (45%)	52 weeks
ECT + doxorubicin	Culine[19]	31	18/31 (58%)	5/11 (45%)	48 weeks
ECT + IFM + CDDP	Kaku	21	9/18 (50%)	2/7 (29%)	47 weeks

median survival duration were shorter for EIP therapy (16 and 47 weeks, respectively) than for IP therapy (21 weeks and 92 weeks).

We could not confirm that addition of ECT yielded any additional long-lasting effects, although differences in background between these treatment groups might exist. In addition, the current study obtained compatible but not superior results in early response and survival in comparison to several previous studies employing multiple drug therapies that included ECT (Table 4) [5, 9–19].

A Subjective symptoms, were alleviated in 29% and remained unchanged in 52% of all cases following EIP therapy and were similar to those following IP therapy, where symptoms were alleviated in 41% and remained unchanged in 41%.When adverse reactions were compared between the EIP and the IP therapy groups (Table 3), the incidence of gastrointestinal symptoms in the EIP therapy group (67%) did not increase compared to that in the IP therapy group (74%). Myelosupression was also comparable to that observed with IP therapy. One patient from the EIP therapy group developed deep venous thrombosis, and another exhibited myocardial infarction. These 2 cases indicate the need for care in monitoring for coagulation and vascular occlusion with EIP therapy.

Unfortunately, EIP therapy demonstrated no obvious advantages over IP therapy in this study. In the treatment of HRPC, the necessity for long-lasting activity remains. A new regimen that includes a multi-descriptional approach should be developed, such as a combined immunogene therapy which can be switched to maintenance therapy.

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