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Treatment of advanced hormone-refractory prostate carcinoma with a combination of etoposide, pirarubicin and cisplatin

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Abstract A total of 20 patients with hormone-refractory prostate carcinoma entered a pilot study of combination chemotherapy based on the EAP (etoposide, Adriamycin and cisplatin) regimen, in which Adriamycin was replaced by pirarubicin, a less cardiotoxic derivative of Adriamycin. The response was assessed by criteria modified from those of the National Prostatic Cancer Project: prostate-specific antigen was employed instead of acid phosphatase. Of 18 evaluable patients, 6 achieved a partial response, 5 had stable disease, and in 7 the disease had progressed during therapy; thus, the overall response rate was 33.3% [95% confidence interval (CI) 11.5–55.1%]. Significant pain alleviation and performance status improvement were obtained in 5 of 12 patients (41.7%; CI 13.8–69.6%) and 3 of 13 patients (23.1%; CI 0.2–46.0%), respectively. Although myelosuppression was moderate to severe, no chemotherapy-related deaths or bacteriologically documented sepsis occurred; nor was there any clinical cardiotoxicity. All the responding patients received maintenance chemotherapy with etoposide thereafter. At present, the median duration of response is 33 weeks (range: 23–91 weeks) and the median survival period for all patients is 42 weeks (range: 27+ –136 weeks), with 12 deaths. In spite of the small number of patients treated, these results suggest that this chemotherapy regimen is active in advanced hormone-refractory prostate carcinoma.

Key words Prostate cancer
Hormone-refractory prostate carcinoma · EAP regimen

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Introduction

The initial response to hormonal maneuvers in untreated stage D prostate carcinoma is usually about 80%. However, the disease will ultimately progress, and virtually all patients develop hormonal resistance. Thus, many clinical trials with cytotoxic chemotherapy have been performed in the search for the best means of treating hormone-refractory prostate carcinoma, and several single agents, such as cyclophosphamide (CPM), Adriamycin (ADM) and cisplatin, have been shown to exhibit activity [4]. The objective response with such agents is generally insufficient, however, and no measurable impact on survival has been obtained. There also seems to be no combination chemotherapy that is superior to single-agent therapy [4]. Thus, there is no clearly optimal chemotherapeutic regimen for the treatment of hormone-refractory prostate carcinoma.

A combination of etoposide, ADM and cisplatin (EAP) has recently been shown to be quite effective in the treatment of advanced gastric carcinoma [10]. Cisplatin has a synergistic action with etoposide [1, 13] and ADM [14] in experimental tumors. There is also a lack of cross-resistance between cisplatin and ADM and between cisplatin and etoposide [14, 15]. Thus, although etoposide exhibits little single-agent therapeutic activity for prostatic carcinoma [18], it appeared worthwhile to assess the efficacy of EAP for the treatment of hormone refractory prostate carcinoma. Since patients with prostatic carcinoma

Table 1 Patients' characteristics and response to ETP chemotherapy (*LN* lymph node; *HT* hormone therapy; *RT* radiation therapy; *CT* chemotherapy; *EMP* estramustine phosphate; *CISCA* cyclophosphamide + Adriamycin + cisplatin)

Case no.	Age (years)	PS	Histological differentiation	Metastatic site	Duration of HT (months)	RT	CT	Response/duration (weeks)	Survival (weeks)
1	63	2	Good	Bone	41	–	NK121	PR/91	110
2	75	0	Poor	LN	62	–	–	PR/40	87
3	54	0	Moderate	Bone	5	+	EMP	PR/38	46
4	77	2	Poor	Lung, LN, bone	27	–	EMP	PR/28	42
5	75	1	Poor	Lung, bone	2	–	UFT	PR/23	34
6	69	1	Moderate	Bone	5	–	–	PR/27+	27+
7	68	1	Poor	Bone	30	–	EMP	OS/34	136
8	61	1	Moderate	Bone	24	–	Cisplatin	OS/73	87+
9	57	1	Poor	Bone	11	–	CISCA, EMP	OS/27	39+
10	83	1	Poor	Bone	58	–	–	OS/35+	35+
11	66	0	Poor	Bone	28	–	EMP	OS/29+	29+
12	65	0	Poor	Bone	90	–	CISCA	PD	55
13	75	0	Poor	Bone	25	–	EMP	PD	46
14	59	2	Poor	Bone	15	–	–	PD	43
15	81	2	Poor	Bone	24	–	–	PD	41
16	62	2	Poor	LN, bone	2	–	–	PD	34
17	60	1	Moderate	Bone	43	+	EMP	PD	33+
18	74	2	Moderate	Lung, LN, bone	125	+	–	PD	31

are usually elderly and are often suffering from concomitant cardiovascular disease, pirarubicin (THP-ADM), a novel derivative of ADM with superior or nearly equivalent cytotoxic activity [6, 17] but lower cardiotoxicity [2, 3, 13, 14] was used instead of ADM in this study.

Patients and methods

The eligibility criteria for the study included metastatic prostate carcinoma that had progressed following hormonal therapy, a performance status (WHO score) of 0–2, a life expectancy of at least 3 months, and an adequate general condition. The progression of prostate carcinoma was assessed basically according to the criteria of the National Prostatic Cancer Project (NPCP) [9]. An increase in serum prostatic acid phosphatase (PAP) or prostate-specific antigen (PSA) alone was not considered an indication of progression. Since there may be no useful treatment left for patients with prostate carcinoma that has progressed following hormonal therapy and chemotherapy including cisplatin and/or ADM, even patients in this category were not deemed ineligible, as we expected a synergistic action or a lack of cross-resistance of drugs used for ETP chemotherapy, as mentioned in the Introduction [1, 13–15]. When patients entered on trial, complete informed consent was obtained from each, and all patients were evaluated by physical examination, excretory urography, chest X-ray, bone scan, transrectal ultrasonography, computed tomography, electrocardiogram, creatinine clearance, serum PAP and PSA, and routine biochemical and hematological determinations.

In this preliminary phase II study, we intended to evaluate 18 patients. Since there have been no useful chemotherapeutic regimens for the treatment of hormone-refractory prostate carcinoma, the presence of five (about 30%) or more responses would have been enough to justify calling this regimen promising.

A total of 20 patients were enrolled in this study between February 1991 and February 1993. Two patients were unevaluable for response and toxicity because of protocol violations: a combination of irradiation or estramustine phosphate (EMP). The characteristics of 18 evaluable patients are presented in Table 1. The median age of the patients was 67, ranging from 54 to 83. All the patients had had estrogen therapy or luteinizing hormone-releasing hormone (LH-RH) analogue for a median duration of 28 (range: 2–125) months and/or orchiectomy. Histological examination of the primary tumors revealed that 12 were poorly differentiated adenocarcinoma, 5 were moderately differentiated adenocarcinoma and only 1 was well-differentiated adenocarcinoma. Bone was the most frequent metastatic site (17 of 18 patients). Extraosseous metastasis was present in 5 patients. Eleven patients had received previous systemic chemotherapy (EMP: 6, CPM + ADM + cisplatin + EMP: 1, CPM + ADM + cisplatin: 1, cisplatin: 1, NK121, a novel derivative of cisplatin: 1, UFT: 1). Three patients had received radiation therapy to the whole pelvis. The follow-up ranged from 27 to 136 weeks, with a median of 42 weeks.

Patients received a combination chemotherapy of etoposide, THP-ADM and cisplatin (ETP) according to the EAP chemotherapy regimen schedule for advanced gastric carcinoma reported by Preusser et al. [10]: etoposide, 60 mg/m^2 i.v. on days 4, 5, and 6; THP-ADM, 20 mg/m^2 i.v. on days 1 and 7; and cisplatin, 40 mg/m^2 i.v. on days 2 and 8. The same regimen was repeated every 4 weeks for three courses. In 2 patients of advanced years (cases 10 and 15) and 1 patient with slightly impaired renal functions due to local progression (case 5) the cisplatin dose was reduced by 30%.

Routine biochemical and hematological determinations were performed at least once a week during the chemotherapy treatment, and once a month thereafter. An assessment of the radiological, ultrasonographic and clinical findings was carried out 2 weeks after the third course of chemotherapy, and at 3-month intervals thereafter. The serum PSA and PAP were also determined 2 weeks after each course of chemotherapy, and every month thereafter. The definition of a normalization or more than a 50% decrease of these tumor markers required reproducibility in an examination 1 month later. The objective response was determined 2 weeks after the third course of chemotherapy according to the criteria of the NPCP [9] with modification: PSA was employed instead of acid phosphotase. The subjective response was based on the performance status (PS) and pain was assessed according to the dose of analgesics required.

Responding patients including those with disease stabilization received 25 mg of etoposide every day as maintenance chemotherapy. The durations of the response and survival were measured from the start of treatment.

Results

The responses of 18 evaluable patients at 2 weeks after the third course of chemotherapy are presented in Table 1. No patient exhibited a complete response (CR), while 6 patients were judged as having achieved a partial response

Table 2 Response and patient's characteristics (*PR* partial response; *OS* objectively stable; *PD* progressive disease; *PS* performance status)

Characteristics	Number of patients			
	PR	OS	PD	Total
Age				
<70	3	4	4	11
≧70	3	1	3	7
PS				
0–1	4	5	3	12
2	2	0	4	6
Histological differentiation				
Good	1	0	0	1
Moderate	2	1	2	5
Poor	3	4	5	12
Duration of prior hormone therapy				
<28 months	3	2	4	9
≧28 months	3	3	3	9
Prior chemotherapy				
Yes	4	4	3	11
No	2	1	4	7
Prior radiation therapy				
Yes	1	0	2	3
No	5	5	5	15

(PR), 5 remained objectively stable (OS) and 7 showed progression (PD), giving an overall response rate of 33.3% (95% CI 11.5–55.1%). At present, the median time to progression for all patients is 27 weeks (range: 12–91 weeks), and the median duration of response for responding patients is 33 weeks (range: 23–91 weeks). The responses according to the patients' characteristics are summarized in Table 2. There was no significant difference in the response rate with any patient characteristic; even the previous chemotherapy did not seem to affect response. Of the 4 patients who had had chemotherapy including cisplatin or its new derivative NK121, 1 achieved PR and 2 were OS. If OS patients are included in the responder group, patients with grade 0–1 PS scores and those without previous radiation therapy showed a better response than each counterpart, although the difference was not significant.

In general, metastases in soft tissue such as the lungs or lymph nodes, responded relatively better than those in bone. Of the 4 patients with lymph node metastasis, 3 showed a reduction by more than 50% of the affected lymph nodes, and all 3 of the patients with lung metastasis showed reduction of lesions in the lungs by more than 50%. However, only 2 of the 17 patients with bone metastasis showed a decrease in bone lesions on bone scan and X-ray films. In 11 patients with an elevated serum PAP, it returned to normal in 2, improved to less than 50% in 2, remained stable in 2, and increased by more than 25% in 5. In 13 patients with elevated serum PSA, on the other hand, it returned to normal in 2, improved to less than 50% in 1, remained stable in 5, and increased by 25% or more in 5. At present, the median survival period for all patients is 42 weeks (range: 27+ –136 weeks), with 12 deaths. At entry, 12 patients complained of bone pain and required analgesics. During the chemotherapy, however, bone pain disappeared in 5 patients, and they required no analgesics for the median duration of 32 weeks (range: 14+ –72 weeks). Of the 5 patients with pain alleviation, 3 showed PR and the remaining 2 had OS at 2 weeks after the third course of chemotherapy. Furthermore, 2 of the 5 patients showed normalization of elevated PSA and definitely decreased density of blastic lesions on bone scan, although the remaining 3 had stable PSA and no change on bone scan. WHO PS scores improved in 3 of 13 patients with more than grade 1 PS scores at entry.

Table 3 Severity and incidence of toxicities

Toxicity	Number of patients experiencing toxicity of grade (WHO scale)				
	0	1	2	3	4
Anemia	1	3	4	8	2
Leukopenia	1	4	5	7	1
Thrombocytopenia	6	2	2	4	4
GOT/GPT	15	3	0	0	0
Nausea/vomiting	7	6	3	2	0
Alopecia	16	2	0	0	0
Mucositis	17	1	0	0	0

Toxicity was evaluated in all 18 eligible patients. The major adverse effect was myelosuppression (Table 3). Ten patients had WHO grade 3–4 anemia, and 8 patients had grade 3–4 leukopenia and/or thrombocytopenia. The gastrointestinal toxicity was generally mild, and there was no clinical cardiotoxicity. None of the 18 patients died of sepsis or had to be withdrawn from the study because of any adverse effects.

Discussion

This trial was conducted to examine the usefulness of a modification of EAP chemotherapy [10], ETP, for advanced hormone-refractory prostate carcinoma. The modifications from EAP were as follows: (1) etoposide was reduced to about 50% to avoid severe myelosuppression; and (2) ADM was replaced by THP-ADM, a less cardiotoxic derivative of ADM.

The overall response rate was 33.3% (95% CI, 11.5–55.1%) of PR according to the modified NPCP criteria [9]. If disease stabilization is included in the responses, the response rate is 61.1% (95% CI, 38.6–83.7%); a high response rate was observed in patients with good PS rather than in those with poor PS. Our relatively high response rate may reflect the high overall response rate or high CR rate of EAP administered for advanced gastric carcinoma [10].

Recently, it has been demonstrated that a neuroendocrine transformation, which is characterized pathologically by the appearance of small cell carcinoma, occurs in patients with advanced prostate carcinoma [5, 16]. Conventional chemotherapy that is effective against small cell neuroendocrine carcinoma of the lung might also be useful

against small cell neuroendocrine carcinoma of the prostate [5, 16]. Moertel et al. [8] reported that combination of cisplatin and etoposide was particularly effective for anaplastic neuroendocrine carcinoma. Although we have no histological data of metastatic lesions in this study, such a transformation may partly account for our high response rate.

Walther et al. [18] reported that in a phase II study on 36 patients with hormone-refractory prostate carcinoma etoposide achieved PR in only 1 case and disease stabilization in 4. It was concluded that etoposide thus had a minimal single-agent therapeutic effect on prostate carcinoma. On the other hand, Merrin et al. [7] reported that of 45 patients with hormone-refractory prostate carcinoma treated with cisplatin, 19 achieved PR and 6 showed disease stabilization, although this high response rate was not confirmed by Yagoda et al. [19] or by Qazi and Khandekar [11]. A phase II study of THP-ADM on 21 patients with hormone-refractory prostate carcinoma showed only 1 PR with a decrease in PSA, and 11 of disease stabilization [12]. The proportion showing normalization or decrease by more than 50% of PSA in this study (3 out of 13 patients) is higher and cannot be explained by the effect of THP-ADM alone. In any event, a combination of these three agents, ETP, seems to offer a better response than any of them as a single agent, although it may be difficult to compare the various response rates objectively, since the criteria for eligibility, evaluability and response are not always identical. The response rate of our ETP was, moreover, higher than that of most other single agents or combinations listed in the review by Eisenberger [4].

Either pain alleviation, an improvement of PS or a decrease of PSA may be obtained by the administration of steroids alone in patients with hormone-refractory prostate carcinoma. In this study, 5 of the 18 evaluable patients received methylprednisolone as an antiemetic for cisplatin. However, the improvement of those parameters were not always associated with the administration of methylprednisolone; methylprednisolone was not given to 2 of 5 patients with pain alleviation, to 1 of 3 patients with an improvement of PS or to 1 of 3 patients with a decrease in PSA. In the patients who received methylprednisolone, the drug was only given on the day of cisplatin administration, and the dose was quite limited (250–500 mg per person per day). Furthermore, the pain alleviation continued for a median duration of 32 weeks, which was much longer than the total duration of ETP chemotherapy (12 weeks). With regard to PSA, the reproducibility of either a normalization or more than a 50% decrease was confirmed at an examination 1 month later. Therefore, the pain alleviation, the improvement of the PS and the reduction of PSA obtained in this study all seemed to be due to the ETP chemotherapy itself rather than related to the administration of steroids as an antiemetic.

In spite of a reduction of the etoposide dosage compared with the original EAP regimen, moderate to severe myelosuppresion did occur in about half the patients. However, neither treatment-related death nor bacteriologically documented sepsis occurred. None of our patients had any hemorrhagic side effects, but thrombocytopenia was considered to be a significant adverse effect in this regimen. Cardiotoxicity in relation to THP-ADM was not observed in any of the patients, and the gastrointestinal toxicity appeared to be tolerable.

The population treated with our ETP regimen had a relatively high incidence of extraosseous metastasis (5 of 18 patients). Moreover, 11 patients had received chemotherapy and 3 patients had had radiation therapy prior to this treatment. Most of the patients can therefore be considered to be relatively far-advanced cases. Nevertheless, the median survival of our patients was rather higher than that of most other chemotherapy regimens listed in the review by Eisenberger [4]; of course it may be difficult to compare the survival indiscriminately. Furthermore, since 6 patients, including 1 patient with PR and 4 with disease stabilization, are still alive, median survival of the patients is expected to lengthen with further follow-up.

In summary, these results suggest that ETP is an active combination in patients with hormone-refractory prostate carcinoma. As Eisenberger [4] mentioned with respect to chemotherapy for prostate carcinoma, its use may be recommended in patients with relatively good PS if care is taken in regard to myelosuppression.

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