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SESSION II

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Chemotherapy for endocrine-therapy-refractory prostate cancer

Abstract The effects of various chemotherapy regimens on endocrine-therapy-refractory prostate cancer were examined in 64 patients. Chemotherapy was started from the first evidence of relapse. The regimens of the initial chemotherapy were as follows: cisplatin (CDDP, 4 cases) and ifosfamide (4 cases) were given as single agents and vincristine, ifosfamide, and peplomycin (VIP, 8 cases); cyclophosphamide, doxorubicin, and CDDP (CAP, 14 cases); ifosfamide, doxorubicin, and CDDP (IAP, 24 cases); and etoposide, doxorubicin, and CDDP (EAP, 10 cases) were given as combinations. On the basis of the results, the patients were divided into two groups: single agents plus VIP and other combinations. In the CAP, IAP, and EAP groups, the cause-specific survival was similar, and the survival of these groups was longer than that of the single agents plus VIP group. Since patients with a long duration between the start of endocrine therapy and the start of chemotherapy were contained in the CAP, IAP, and EAP groups, comparison was performed without these cases. No difference was found between the two groups, suggesting that no superior regimen was found. The short-term effect was evaluated on the basis of the changes observed in prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) levels at 3 months after the start of chemotherapy, and patients showing a complete response, partial response, or no change on any of the regimens exhibited longer survival than did those with progressive disease. Since the PSA doubling time estimated before the chemotherapy correlated with the change in the PSA values due to the chemotherapy, the rate of proliferation of the tumor influenced the effect of the chemotherapy. Thus, this finding suggests that slowly growing cancers show a better response to chemotherapy than do rapidly proliferating ones.

Key words Prostate cancer · Endocrine relapse · Chemotherapy

Introduction

Although 70%–80% of prostate cancer patients initially respond to endocrine therapy, more than half of the responders finally develop a refractory state [19]. Thus, there are many reports concerning chemotherapy of endocrine-therapy-refractory prostate cancer. However, there seems to be no effective chemotherapy available for these cancers [7, 9, 20, 22].

Our clinic has treated cases of endocrine-therapy-refractory prostate cancer with chemotherapy. To develop more effective chemotherapy, the present study was performed to analyze the results in detail, with special attention being paid to the change in the serum prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) levels so as to gauge the short-term effects of treatment.

Patients and methods

A total of 64 patients diagnosed as having endocrine-therapy-refractory prostate cancer at Chiba University Hospital between 1979 and 1992 were investigated in the present study. According to the American system, the clinical stage at the start of endocrine therapy was C, 11 cases; D1, 5 cases; and D2, 48 cases. The endocrine therapy consisted of castration plus 250–500 mg diethylstilbestrol diphosphate daily followed by 30–60 mg hexesterol or 1.0–1.5 mg ethynylestradiol daily in 44 cases. Among these, 10 patients were changed to 100 mg chlormadinone acetate daily because of side effects. For 12 patients, 100 mg chlormadinone acetate daily was used from the start instead of estrogen due to cardiovascular complications. In addition, castration and 150–300 mg anandorone daily followed by chlormadinone acetate

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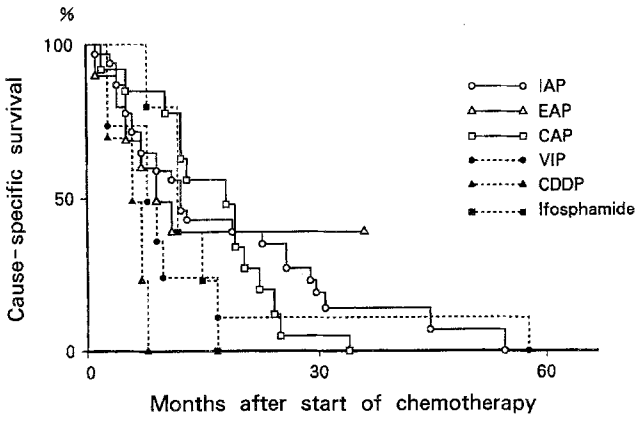

Fig. 1 Cause-specific survival after the start of chemotherapy according to each regimen

was employed in four patients, initial radiation therapy followed by endocrine therapy after relapse was used in three patients, and total prostatectomy and endocrine therapy were applied in one patient in this study. Patients showing a performance status of 0–3 according to WHO criteria without developing serious complications received systemic chemotherapy.

The age of the patients at relapse ranged between 49 and 81 years (mean, 70.9 years). The sites of relapse at the start of chemotherapy were bone in 41 cases, local regrowth in 16 cases, both in 3 cases, and an increase in PAP in 4 cases. Administration of the hormonal drugs was discontinued when relapse was evident. The interval between the start of the endocrine therapy and the start of chemotherapy ranged from 14 to 138 months (mean, 28.1 months).

The initial chemotherapy regimens were as follows: cisplatin (CDDP, 20 mg × 5 days) and ifosfamide (2 g × 5 days) were given as single agents and vincristine (1 mg × 2 days), ifosfamide (30–50 mg/kg × 3 days), and peplomycin (5 mg × 6 days, VIP); cyclophosphamide (100 mg × 5 days), doxorubicin (30 mg × 1 day), and CDDP (50 mg × 1 day, CAP; ifosfamide (2 g × 3 days), doxorubicin (30 mg × 1 day), and CDDP (50 mg × 1 day, IAP); and etoposide (30–40 mg/m^2 × 5 days), doxorubicin (30–40 mg/m^2 × 1 day), and CDDP (10–15 mg/m^2 × 5 days, EAP) were given as combination therapies.

The serum PSA [12] and PAP levels were determined with Eiken kits (radioimmunoassay with two antibodies; Eiken Chemical Co., Tokyo, Japan). To evaluate the short-term effects of the chemotherapy, the changes in PSA and PAP levels at 3 months after chemotherapy relative to the pretreatment levels were calculated and classified as a complete response (CR, normalization), a partial response (PR, greater than a 50% reduction), progressive disease (PD, greater than a 25% increase), or no change (NC, intermediate between PR and PD). To estimate the PSA doubling time, the change in PSA was serially depicted as semilogarithmic plots.

The cause-specific survival was calculated after the start of the chemotherapy [14]. Statistical analysis of the survival was performed by the generalized Wilcoxon test. Comparisons between two groups were performed by a two-sample *t*-test with Welch's correction and the chi-square test.

Results

Clinical course after the start of chemotherapy

Six chemotherapy regimens were performed over the years: single-agent, 1979–1981 (8 cases); VIP, 1981–1983 (8 cases); CAP, 1983–1986 (14 cases); IAP, 1987–1990 (24 cases); and EAP, 1990–1992 (10 cases). The numbers of courses given for the single agents and the VIP, CAP, IAP, and EAP combinations were 1–5 (mean, 2.1), 1–8 (mean, 3.1), 1–8 (mean, 3.6), 1–8 (mean, 2.5), and 1–4 (mean, 2.0), respectively. Three cases were subsequently changed from CDDP to ifosfamide.

The cause-specific survival from the start of the chemotherapy was depicted for each regimen (Fig. 1). CAP, IAP, and EAP showed similar cause-specific survival, and these three regimens seemed to achieve longer survival than did the single agents or VIP. Therefore, the results were divided into two groups: the single agents plus VIP and the other

Table 1 Patients' characteristics at the start of chemotherapy

	CDDP, Ifosfamide, VIP (n = 16)	CAP, IAP, EAP (n = 48)	
Previous treatment:			NS
Castration (Cast) + estrogen	14	30	
Cast + antiandrogen	1	15	
Cast + radiation + estrogen/antiandrogen	1	2	
Total prostatectomy + cast + antiandrogen		1	
Age (years)	68.9 ± 9.9	72.4 ± 6.4	NS
Duration from initial treatment to chemotherapy (months)	20.1 ± 12.8	37.4 ± 39.7	$P < 0.05$
Previous use of oral anticancer drug:			NS
Yes	4	11	
No	12	37	
Hemoglobin	12.4 ± 1.2	12.4 ± 1.9	NS
Performance status:			NS
0	0	3	
1	6	22	
2	6	17	
3	3	5	
4[a]	1	1	

[a] Due to pain from bone metastases

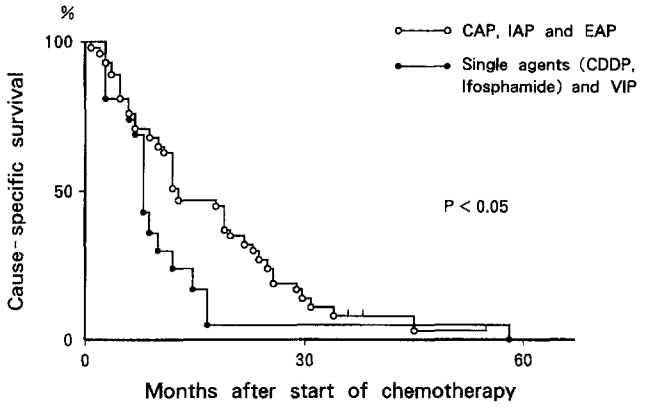

Fig. 2 Cause-specific survival after the start of chemotherapy in the CAP/IAP/EAP group and the single-agent plus VIP group

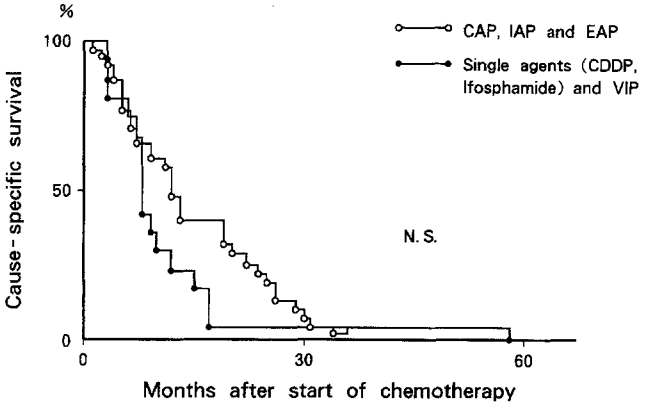

Fig. 3 Cause-specific survival after the start of chemotherapy in the CAP/IAP/EAP group and the single-agent plus VIP group. Eight cases from the former group, with a long duration between the start of the endocrine therapy and the start of the chemotherapy, were omitted from the data of Fig. 2

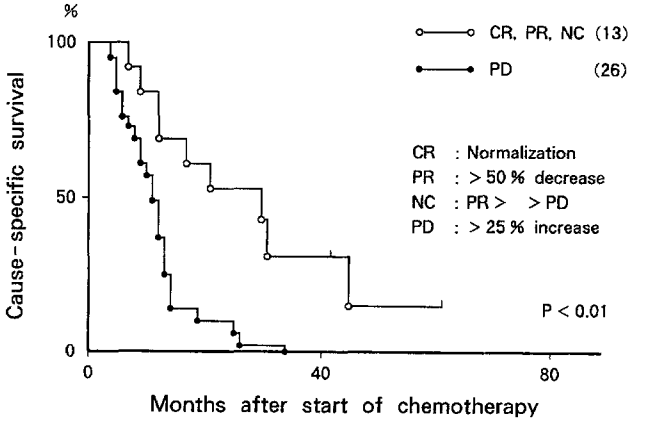

Fig. 4 Cause-specific survival after the start of chemotherapy in responders (CR, PR, NC) and nonresponders (PD) as evaluated on the basis of the PSA and PAP levels measured at 3 months after treatment

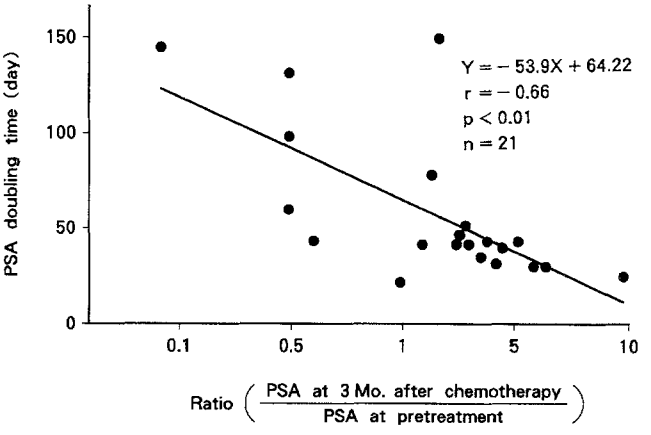

Fig. 5 Relationship between the PSA doubling time and the ratio of the PSA level at 3 months after chemotherapy to the pretreatment level

combination regimens (Fig. 2). Although the survival of the latter group seemed to be superior, this group contained eight cases in which the interval between the start of the endocrine therapy and the start of the chemotherapy was long (55–138 months, Table 1). When the cause-specific survival of the two groups were compared without these eight cases, there was no difference between them (Fig. 3), suggesting that none of the chemotherapy regimens provided superior survival.

Influence of short-term changes in PSA and PAP on prognosis

The changes in PSA and PAP levels at 3 months after the start of chemotherapy were examined in 39 patients to evaluate the short-term effect of treatment. The effect of the therapy was judged as CR, PR, NC, and PD in 4, 5, 4, and 26 patients, respectively. The survival of the CR+PR+NC cases was longer than that of the PD cases (Fig. 4).

Relationship between PSA doubling time and changes in PSA after chemotherapy

The PSA doubling time at relapse was measured for 21 cases, and the values were compared with the therapeutic effect evaluated from the ratio of the PSA level at 3 months after treatment to the pretreatment level. The PSA doubling time ranged between 19.6 and 144 days. The ratio of the change in PSA levels ranged between 0.08 and 9.29. The relationship between these two values was evident (Fig. 5), suggesting that slowly growing cancers showed a tendency to respond to chemotherapy.

Side effects of chemotherapy

Serious toxicity was observed in the ifosfamide and VIP groups, including liver dysfunction and lung fibrosis. All side effects recovered after discontinuation of the chemotherapy. Nausea and vomiting occurred in almost all

Table 2 Side effects of chemotherapy

	CDDP, Ifosfamide, VIP (n = 16)	CAP, IAP, EAP (n = 48)
Lung fibrosis	4	0
Hemologic cystitis	2	1
Leukopenia: <2,000/mm^3	5	8
Pancytopenia[a]	2	2

[a] WBC, <2,000/mm^3, hemoglobin <8.0 g/dl; platelets, <50,000/mm^3

patients who were treated with CAP, IAP, and EAP, but the treatments were nevertheless well tolerated (Table 2).

Discussion

Although the efficacy of chemotherapy in endocrine-therapy-refractory prostate cancer remains controversial, combination chemotherapy has recently been widely used in these patients [3, 4, 6, 11, 13, 18]. To date, alkylating agents (cyclophosphamide [11] and ifosfamide [8]), antimetabolites (5-fluorouracil [3, 11, 13]), antifolate agents (methotrexate [15]), antibiotics (mitomycin C [10], doxorubicin [3, 4, 11], and peplomycin), plant alkaloids (vinblastine [5] and etoposide [21]), and CDDP [6] have been used for combination regimens. The response rates to the chemotherapy, however, have been low in many reports. According to National Prostate Cancer Project (NPCP) criteria, the rates of partial response (PR) plus stable disease (SD) were reported to be 32%–59% for cyclophosphamide; 57%–84% for doxorubicin (with or without cyclophosphamide); 21%–36% for CDDP [7]; 68% for combinations of CDDP, doxorubicin, and cyclophosphamide [6]; and 43%–47% for combinations of doxorubicin, mitomycin C, and 5-fluorouracil [4]. Responders showing SD greatly outnumbered PR cases. In the present study, six regimens were given to patients with endocrine-therapy-refractory prostate cancer, and similar efficacy was recorded for each treatment. Thus, it can be said that none of the regimens was clearly superior.

An important issue is whether a short-term response to chemotherapy prolongs survival or not. In the present study, the 50% survival time after the start of the chemotherapy was calculated as 13 months for all of the patients. However, the 50% survival time for patients showing CR+PR+NC as evaluated on the basis of the PSA and PAP values at 3 months after therapy was 30 months; therefore, these responders showed prolongation of survival. In contrast, patients with PD showed 11 months as their 50% survival time, and this duration is similar to that observed after relapse without effective chemotherapy [16]. Responders showing PR and SD accounted for one-third of the total number of patients included in this study, but these patients got benefit from the chemotherapy regimens.

When the effects of various chemotherapeutic regimens are compared, patients' characteristics such as the performance status seem to be important [1]. Moreover, the biological properties of prostate cancer cells are extremely variable, and this profoundly influences the prognosis [7]. It has been reported that the interval between the initial endocrine therapy and relapse correlates with the survival of patients [22]. When the interval is considered as a property of the cancer cells, the obvious difference in survival may be diminished as shown in the present study.

The PSA doubling time in patients with untreated prostate cancer has recently been reported to be of value [17]. Patients with a longer PSA doubling time have shown a better response [2]; thus, the doubling time may be a good indicator for predicting the effect of chemotherapy. Comparison of the chemotherapeutic effect requires strict stratification of the host characteristics and tumor properties.

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