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SESSION II

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# Chemo-endocrine therapy for prostate cancer with bone metastasis

**Abstract** We analyzed the clinical effects of initial chemoendocrine therapy on 31 prostate cancer patients with bone metastasis. These patients had been newly diagnosed between 1983 and 1991 and had received no previous therapy. As endocrine therapy, the patients received 1 mg ethynylestradiol daily with or without orchiectomy. In addition, they received three courses of chemotherapy consisting of 20 mg/m$^2$ cisplatin given on days 1, 3, and 5 and 20 mg/m$^2$ Adriamycin or 40 mg/m$^2$ epirubicin given on day 5. Subsequently, for maintenance therapy, the patients received 1 mg ethynylestradiol and 150 mg 5-fluorouracil [or 300 mg tegafur plus uracil (UFT)] daily. Patients given our regimen of chemoendocrine therapy had a significantly better prognosis than did the controls treated with endocrine therapy alone ($P = 0.05$), although treatment was not randomized. The cause-specific survival rates at 5 years for the chemoendocrine-therapy patients and the control group were 65.4% and 37.4%, respectively. A multivariate analysis of possible prognostic factors, i.e., age, histological grade, prostatic acid phosphatase, tumor-related pain, the extent of disease (EOD) on bone scan, and the type of initial treatment, confirmed that the initial treatment ($P = 0.03$) and the EOD grade ($P = 0.05$) had a significant effect on survival. On the basis of these results, it is necessary to carry out a randomized trial to compare our chemoendocrine regimen with endocrine therapy alone in untreated patients with advanced prostate cancer.

**Key words** Prostate cancer · Chemotherapy · Endocrine therapy

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## Introduction

As treatment of metastatic prostate cancer, several randomized trials have evaluated the effectiveness of adding chemotherapy to initial endocrine therapy. In terms of overall survival, however, three studies of the National Prostatic Cancer Project (NPCP) [3, 9, 10] and a study of the Southwest Oncology Group [11] found that such initial chemoendocrine therapy did not yield statistically significant results. In those trials, cyclophosphamide, estramustine phosphate, 5-fluorouracil, methotrexate, and Adriamycin were used as the chemotherapeutic agents.

In contrast to those findings, since 1983 we have treated advanced prostate cancer patients with chemoendocrine therapy using cisplatin, Adriamycin, and 5-fluorouracil, and the outcomes of these patients with respect to survival have been favorable. Herein, we report on the effects of this initial chemoendocrine therapy on prostate cancer patients with bone metastasis and discuss the efficacy of this therapy.

## Patients and methods

We analyzed the clinical effects of chemoendocrine therapy in 31 prostate cancer patients with bone metastasis. These patients had received no previous therapy and underwent our chemoendocrine regimen after their cancers had been diagnosed between 1983 and 1991. Their characteristics are shown in Table 1. All patients received endocrine therapy that consisted of the administration of 1 mg ethynylestradiol daily, and a majority of them also underwent bilateral orchiectomy. In addition, they received 20 mg/m$^2$ cisplatin on days 1, 3, and 5 and 20 mg/m$^2$ Adriamycin or 40 mg/m$^2$ epirubicin on day 5. This cycle was repeated three times at 1- or 2-week intervals. Subsequently, for maintenance therapy, the patients received 1 mg ethynylestradiol and 150 mg 5-fluorouracil [or 300 mg tegafur plus uracil (UFT)] daily.

The status of each patient was monitored before the start of treatment, 3 months after the initial therapy, and then every 6 months. Follow-up investigations included a digital rectal examination, transrectal ultrasonography, monitoring of the prostatic acid phosphatase (PAP) and alkaline phosphatase (ALP) serum levels, and other routine laboratory tests. Bone scans and/or bone X-rays were performed yearly

**Table 1** Patients' characteristics (*N* Upper limit of the normal range)

| Mean age: 68 years (range, 55–82 years) | |
|---|---|
| | Number of patients |
| Histological grade: | |
| Well differentiated | 3 (9.8%) |
| Moderately differentiated | 16 (51.6%) |
| Poorly differentiated | 12 (38.7%) |
| Prostatic acid phosphatase: | |
| ≦ 1 × N | 1 (3.2%) |
| 1–2 × N | 5 (16.1%) |
| > 2 × N | 25 (80.6%) |
| Pain: | |
| None | 13 (41.9%) |
| Present | 18 (58.1%) |
| EOD grade[a]: | |
| I | 7 (22.6%) |
| II | 10 (32.3%) |
| III | 9 (29.0%) |
| IV | 5 (16.1%) |

[a] EOD grade: the number of bone metastases is <6 units in grade I, 6–20 units in grade II, >20 but less than "super scan" in grade III, and "super scan" or its equivalent in grade IV

or when indicated. The extent of disease (EOD) on bone scanning was graded semiquantitatively by the method of Soloway et al. [12]. The objective response was evaluated at 3 months after the start of treatment according to the response criteria of the National Prostatic Cancer Project [8]. Also, toxicity was assessed on the basis of WHO grades [7].

For survival evaluation in these patients, 43 prostate cancer patients with bone metastasis who had been treated between 1980 and 1989 with endocrine therapy alone served as our controls for reference. The type of treatment was not randomized, and the choice of therapy depended on patient acceptance. Cause-specific survival curves were calculated according to the Kaplan-Meier method [5], and the statistical significance was calculated by the generalized Wilcoxon method [2]. In the cause-specific survival analysis, deaths due to causes unrelated to cancer of the prostate were treated as withdrawals in the same manner as those lost to follow-up. The clinical data of the chemoendocrine-therapy patients and endocrine-therapy group were analyzed by the chi-square test. Furthermore, to determine whether the chemoendocrine therapy influenced survival, multivariate analysis using Cox's proportional-hazards regression model [1] was performed.

## Results

Of the 31 patients treated with chemoendocrine therapy, 8 (25.8%) showed a partial response, 18 (58.1%) showed stabilization of their disease, and 5 (16.1%) showed disease progression as based on NPCP criteria.

**Table 2** Toxicity (*BUN* Blood urea nitrogen)

| | WHO grade/number of patients | | | | |
|---|---|---|---|---|---|
| Toxicity | 0 | 1 | 2 | 3 | 4 |
| Anemia | 12 | 11 | 6 | 2 | 0 |
| Leukopenia | 23 | 2 | 5 | 1 | 0 |
| SGOT/SGPT | 28 | 3 | 0 | 0 | 0 |
| Nausea/vomiting | 16 | 9 | 6 | 0 | 0 |
| Diarrhea | 29 | 2 | 0 | 0 | 0 |
| BUN/creatinine | 30 | 0 | 1 | 0 | 0 |
| Allergy | 30 | 1 | 0 | 0 | 0 |
| Hair loss | 25 | 4 | 2 | 0 | 0 |

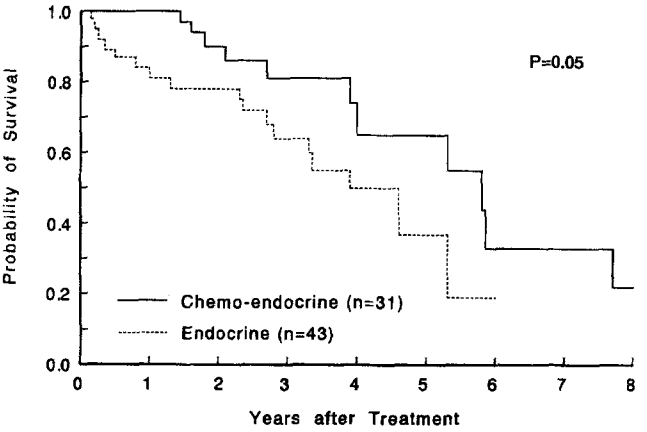


**Fig. 1** Cause-specific survival curves generated for the chemoendocrine-therapy patients and the controls treated with endocrine therapy alone. Patients treated with our chemoendocrine regimen had a significantly better prognosis than did the controls

The data on the toxicity of the induction chemotherapy (i.e., a regimen of three courses of cisplatin plus Adriamycin/epirubicin) are summarized in Table 2. The induction chemotherapy was well tolerated, with only two patients showing WHO grade 3 anemia and one patient developing leukopenia of grade 3. Furthermore, no toxicity except for mild gastritis was seen during the maintenance chemotherapy with 5-fluorouracil or UFT.

The cause-specific survival rates at 5 years for the chemoendocrine-therapy patients and the control group were 65.4% and 37.4%, respectively (Fig. 1). The patients given chemoendocrine therapy had a significantly better prognosis than did those given endocrine therapy alone ($P = 0.05$). However, some differences in the background data between these two groups were noted (Table 3), since the present study was not a prospective randomized trial. The chemoendocrine-therapy patients were younger than those in the control group ($P = 0.004$). Furthermore, there was greater manifestation of pain related to bone metastasis in the chemoendocrine-therapy patients than in the control group ($P = 0.05$).

Table 4 shows the results of the multivariate analysis of the six variables listed in Table 3. Although the patients were not equally distributed with regard to age or pain, these two variables were found to be unimportant in the multivariate survival analysis. Only the type of initial treatment received ($P = 0.03$) and the EOD grade ($P = 0.05$) exerted a significant effect on survival.

## Discussion

This retrospective analysis revealed that patients receiving our regimen of chemoendocrine therapy had a significantly better prognosis than did the controls treated with endocrine therapy alone. Although varied distribution in the patients'

**Table 3** Correlation between the type of treatment and the variables studied in Cox's regression model

| | Treatment | | Chi-square test (*P* value) |
|---|---|---|---|
| | Endocrine | Chemoendocrine | |
| Age (years): | | | |
| <75 | 19 | 24 | 0.004 |
| ≧75 | 24 | 7 | |
| Histological grade: | | | |
| Well differentiated | 9 | 3 | 0.43 |
| Moderately differentiated | 20 | 16 | |
| Poorly differentiated | 14 | 12 | |
| Prostatic acid phosphatase: | | | |
| ≦ 1 × N | 9 | 1 | 0.06 |
| 1–2 × N | 9 | 5 | |
| >2 × N | 25 | 25 | |
| Tumor-related pain: | | | |
| None | 28 | 13 | 0.05 |
| Present | 15 | 18 | |
| EOD grade: | | | |
| I | 13 | 7 | 0.58 |
| II–III | 26 | 19 | |
| IV | 4 | 5 | |

**Table 4** Multivariate analysis of possible prognostic factors in Cox's regression model for patients with prostate cancer with bone metastasis

| Variable | Regression coefficient | Standard error | *t* value[a] | *P* value |
|---|---|---|---|---|
| Initial treatment | –1.163 | 0.508 | –2.291 | 0.03 |
| Age | 0.125 | 0.424 | –0.296 | 0.77 |
| Histological grade | 0.013 | 0.304 | 0.041 | 0.97 |
| Prostatic acid phosphatase | –0.209 | 0.317 | –0.658 | 0.51 |
| Tumor-related pain | 0.149 | 0.486 | 0.306 | 0.76 |
| EOD grade | 0.955 | 0.468 | 2.041 | 0.05 |

a Regression coefficient/standard error

age and the pain caused by the prostate cancer was noted, the difference in the duration of survival detected between these two groups was probably not influenced by these two factors, since they hardly contributed to the outcome in our multivariate survival analysis. The results of this analysis show that the initial chemoendocrine therapy influences the clinical outcome. Furthermore, as had been seen in our previous study [4], the EOD grade was also found to be a significant prognostic factor. Although few reports have supported the use of early chemotherapy, the present encouraging results warrant carrying out a randomized trial to compare our chemoendocrine regimen with endocrine therapy alone in untreated patients with advanced prostate cancer.

Although the chemotherapeutic regimen of cisplatin and Adriamycin/epirubicin resulted in instances of anemia, leukopenia, and nausea/vomiting, most of these adverse reactions were mild enough to be tolerated. Prostate cancer is a disease that affects the elderly, and those who develop bone metastasis most often incur bone marrow metastasis [6]. Since such patients often lack adequate hematopoietic function, they must be carefully followed after the initial chemotherapy.

To determine clearly whether our chemoendocrine regimen is truly effective for patients with advanced prostate cancer, we are now conducting a randomized trial to compare the efficacy of chemoendocrine therapy with that of endocrine therapy alone in patients with newly diagnosed advanced prostate cancer.

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