A prospective, randomized clinical trial was conducted to evaluate the efficacy of endocrine chemotherapy with uracil and tegafur (in a molar ratio of 4:1 [UFT]) in patients with prostate cancer. The study included two

Introduction

Androgen ablation has been an effective and important therapeutic modality in the treatment of prostate cancer since first reported by Huggins et al in 1941.[1] Several studies have demonstrated that androgen ablation delayed death in prostate cancer patients,[2-6] although it could not completely suppress progression of the disease. Because prostate cancer cells are heterogeneous, some prostate cancer cells survive and proliferate even after androgen ablation. Endocrine chemotherapy was developed as a means of killing hormone-independent and hormone-dependent cancer cells simultaneously. Various regimens have been developed as endocrine chemotherapy for prostate cancer since the first report by Merrin et al in 1980.[7-10] Cyclophosphamide (Cytoxan), cisplatin (Platinol), combination chemotherapy with cyclophosphamide plus 5-fluorouracil (5-FU), and estramustine phosphate (Emcyt) have been evaluated as chemotherapeutic modalities. Although response rates of 20% to 84% have been reported, long-term outcomes have not suggested a significant benefit with these regimens.

UFT is an oral antineoplastic drug consisting of uracil and tegafur in a 4:1 molar ratio. Tegafur is a prodrug of 5-FU, being slowly metabolized to 5-FU.[11,12] We combined endocrine therapy with UFT in a prospective, randomized clinical trial to evaluate its efficacy in the treatment of prostate cancer.

Patients and Methods

Inclusion and Exclusion Criteria

Eligible patients had histologically proven adenocarcinoma of the prostate; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3; a serum creatinine level less than 2 mg/dL; an acceptable hepatic function with serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase level less than twice normal; and serum bilirubin level less than 2 mg/dL. Patients with severe cardiovascular diseases, such as uncontrollable congestive heart failure, refractory hypertension, or symptomatic coronary artery disease, or patients who underwent coronary bypass surgery within 6 months of registration were excluded. Patients who received prior or concomitant systemic chemotherapy, hormone ablation, radiation, or biologic response modifiers, or patients who had a history of any neoplasm within the past 5 years were also excluded. From April 1990 to December 1992, 142 patients from 26 institutes were enrolled in this study.

Study Design

Patients with prostate cancer proven by biopsy were asked to submit informed consent. Patients who had undergone castration were randomized to receive 200 mg/day of diethylstilbestrol with or without 400 mg/day of UFT. Both treatments were continued until patients showed progressive disease or became intolerant of the treatment. These patients were removed from this study and treated at the investigator's discretion. All patients are being followed until death. Pretreatment examination included urinalysis; complete blood counts; hepatic function tests; the determination of acid phosphatase and alkali phosphatase levels; a chest x-ray; a bone scan, with skeletal film of abnormal areas; intravenous pyelography; and computed tomography of the pelvis with the use of a contrast medium. The patients were clinically evaluated 4, 8, and 12 weeks after treatment began, as were laboratory studies. Clinical, laboratory, and imaging investigations were
completely performed at 12-week intervals. The National Prostatic Cancer Project criteria were used to evaluate response.[13] Though a bone scan at 12 weeks of treatment was not mandatory, patients with stable disease who did have a scan were followed for an additional 6 weeks if there were one or two new lesions on the scan, at which time a second bone scan was performed. In the absence of evidence of further disease progression, the patient’s condition was considered stable, and therapy was continued with the assigned treatment.

All laboratory reports and patient records were reviewed for quality control.

Statistical Method
Progression-free rate, cancer-specific survival rate, and overall survival rate were calculated using the Kaplan-Meier method and evaluated using the log-rank method.

Results
Of the 142 patients registered for this study, 136 (96%) were eligible. Of the six ineligible patients, four had no objective evidence of prostate cancer and two had a second malignancy. One of the six ineligible patients was assigned to endocrine plus UFT therapy, and five were assigned to endocrine-only therapy. Characteristics of all 136 eligible patients were as follows: The mean age was 75 years (range, 50 to 91); ECOG performance statuses were 0 in 79, 1 in 30, 2 in 18, and 3 in 9 patients. Clinical stages were A2 in 5, B in 13, C in 18, and D in 100 patients. The 18 patients with stage A2 and B disease refused radical prostatectomy or were not indicated for it because of various physical and social reasons. Biopsy of the prostate showed that 49 patients had well-differentiated, 64 had moderately differentiated, and 23 had poorly differentiated carcinomas. Of the 136 patients, 69 were randomly assigned to the UFT group and 67 to the endocrine-only group. There were no significant differences in characteristics between the two arms (Table 1).

As of January 1, 1998, the mean follow-up period was 54.9 months in the UFT group and 47.8 months in the endocrine-only group. The follow-up rate was 88.4% in the UFT group and 86.6% in the endocrine-only group. Forty-five (66.2%) of the 68 patients receiving UFT therapy and 42 (62.7%) of the 67 patients receiving endocrine-only therapy achieved partial responses. Twenty-one patients (30.9%) in the UFT group and 24 patients (35.8%) in the endocrine-only group showed no change. Two patients (2.9%) in the UFT group and one patient (1.5%) in the endocrine-only group showed progressive disease.

The 5-year nonprogression (disease-free) rate was 53.0% in the UFT group and 43.8% in the endocrine-only group (Figure 1). The 5-year cancer-specific survival rate was 67.4% in the UFT group and 49.5% in the endocrine-only group (Figure 2). The 5-year overall survival rate was 47.4% in the UFT group and 35.4% in the endocrine-only group (Figure 3). The study demonstrated improvements in nonprogression, cancer-specific survival, and overall survival in favor of the UFT group, although these improvements were not statistically significant.

Table 2 shows the adverse effects associated with the two study regimens. Peripheral edema and anorexia occurred in both groups. Nausea and vomiting were more frequent in the UFT group (P = .072). However, neither treatment group necessitated cessation or major modification of treatment for these adverse effects. Cerebral vascular disease and ischemic heart disease were also observed, but not with statistically significant differences between groups. Three patients in the UFT group and eight patients in the endocrine-only group discontinued treatment due to vascular disease. Grade 3 anemia was noted in one patient in each group. Grade 3 thrombocytopenia occurred in one UFT-treated patient and in no patient in the endocrine-only group. Twenty-two (31.9%) of the 69 patients receiving UFT therapy and 26 (38.8%) of the 67 patients receiving endocrine-only therapy discontinued further treatment due to adverse effects. There were statistically significant differences in the toxicity profiles between the groups.

Discussion
Androgen ablation is an important and effective therapeutic modality in the treatment of prostate cancer. It is well known, however, that androgen ablation therapy cannot completely suppress progression of prostate cancer. Seventy percent of patients with metastatic prostate cancer completely and partially respond to androgen ablation, but disease progresses in most patients after 1 to 2 years. Cardiovascular complications—sometimes life-threatening—and feminizing side-effects can be associated with castration.[2-6] The 5-year survival rate in prostate cancer after androgen ablation is 30%. Endocrine chemotherapy was developed with the intention of killing hormone-dependent and
hormone-independent cancer cells simultaneously. Some clinical trials of endocrine chemotherapy for prostate cancer, mainly involving cyclophosphamide, cisplatin, 5-FU, and estramustine have been described previously (Table 3).[6-10] The most effective agents, however, are still unclear, and the efficacy of endocrine chemotherapy has not been proven.

UFT was developed in Japan 15 years ago and has been shown effective in colorectal, breast, and lung cancers, with minimal toxicity to patients. In addition, UFT is convenient for long-term administration. Based on these benefits, we chose to study the activity of UFT as a supplement to endocrine chemotherapy for the treatment of prostate cancer.

Statistically significant differences in response rates between endocrine plus UFT therapy and endocrine-only therapy were not demonstrated in this study. The nonprogression rate was better in the UFT group (P = .114). Additionally, the overall survival rate favored endocrine plus UFT therapy (P = .177). However, these figures may have been significantly influenced by a large number of inevitable deaths of aged patients: Eight patients over 85 years were included in this study, of which six patients were in the UFT group and two were in the endocrine-only group. Mean life expectancy for an 85-year-old man is about 5 years. Enrollment of patients over 85 years in any clinical study has been questioned from both statistical analysis and ethical viewpoints.

We should take a patient’s age into account as an important stratification factor. In addition, the endocrine therapy in both treatment arms of this study involving castration and the long-term administration of diethylstilbestrol caused cardiovascular disease, which often resulted in death. This might have contradicted the beneficial effect of UFT. UFT has been associated with adverse effects, such as anorexia, nausea, vomiting, diarrhea, and myelosuppression. In this study, nausea and vomiting were often observed in the UFT group, but were most often tolerable, not necessitating treatment modification. In the UFT group, four of the 69 patients experienced grade 3 nausea, anorexia, thrombocytopenia, and anemia.

**Conclusion**

Endocrine chemotherapy with UFT is a safe and well-tolerated regimen for patients with prostate cancer. This regimen might be effective for prostate cancer and should be evaluated further.

**References:**


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