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Original article

Feasibility of metronomic chemotherapy with tegafur-uracil, cisplatin, and dexamethasone for docetaxel-refractory prostate cancer

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Abstract

Objectives: To evaluate the efficacy of tegafur–uracil (UFT), a prodrug of 5-fluorouracil, plus cisplatin and dexamethasone in patients with docetaxel-refractory prostate cancers.

Methods: Twenty-five patients with docetaxel-refractory prostate cancer were administered oral UFT plus intravenous cisplatin (UFT-P therapy) and dexamethasone. Treatment responses were assessed monthly via prostate-specific antigen (PSA) level measurements. Treatment-related adverse events and overall survival were also assessed.

Results: UFT-P therapy resulted in decreased PSA levels in 14 (56%) patients and increased PSA levels in 11 (44%). In patients with increased PSA levels, 7 (64%) of the 11 patients displayed decreased PSA doubling times. The UFT-P therapy response rate was 84% (21/25 patients). Imaging studies revealed that tumor shrinkage during UFT-P therapy occurred in 1 patient in whom bilateral hydronephrosis caused by lymph node metastasis improved. The median survival time from docetaxel initiation was 36 months. In UFT-P-treated patients, the median PSA progression and overall survival times were 6 and 14 months, respectively. UFT-P treatment-related adverse events were mild diarrhea, general fatigue, and anorexia. Treatment was not discontinued for any of the patients. UFT-P therapy did not cause serious hepatic or renal dysfunction or pancytopenia.

Conclusions: UFT-P therapy is a safe and effective treatment for patients with docetaxel-refractory prostate cancer, although large-scale, multicenter, prospective studies are needed to validate these findings.

Key words: prostate cancer, chemotherapy, tegafur–uracil (UFT), cisplatin, dexamethason

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Introduction

In Japan, prostate cancer is a common malignant tumor, and the global prevalence of prostate cancer is increasing. Forecasts for 2020, predict a 2.8-fold rise in prostate cancer mortality rates, compared with those in 2000[1]. The mainstay treatments for prostate cancer include surgery or radiotherapy. However, patients with advanced metastatic cancer, or those with metastases or recurrence after surgery or radiotherapy, often undergo androgen deprivation therapy (ADT). ADT is effective in such patients, and its use has increased worldwide[2, 3]. However, patients undergoing ADT eventually develop castration-resistant prostate cancer (CRPC)[4]. The efficacy of docetaxel-based systemic chemotherapy for CRPC was recently reported[5, 6]. However, nearly all patients with CRPC develop docetaxel-refractory prostate cancer, characterized by increasing serum PSA levels. Reports on drug therapies for such patients are scarce, and effective treatment protocols have not been established.

Tegafur–uracil (UFT) is a prodrug combination, in which tegafur is converted to cytotoxic 5-fluorouracil (5-FU) *in vivo*. In this combination, uracil potentiates the antitumor activity of tegafur[7, 8] by enhancing the bioavail-

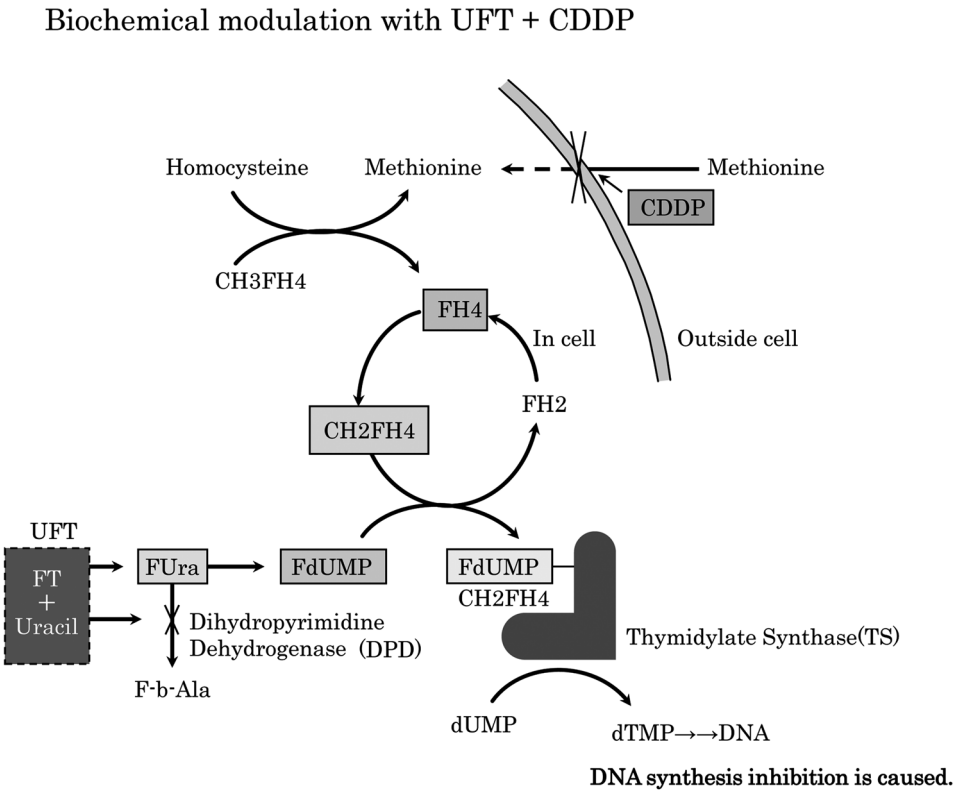

Figure 1 When uptake of methionine into the cell is obstructed by cisplatin, methionine synthetase is induced and folic acid metabolism is accelerated. Consequently, the number of deoxidizing folic acids (FH4, CH2FH4) increases, the production life of the ternary complex (FdUMP+CH2FH4+TS) increases, and the cytotoxicity reaction of UFT (DNA synthesis inhibition) is reinforced. FH4; tetrahydrofolate, CH2FH4; methylenetetrahydrofolate, TS; thymidylate synthase, FdUMP; fluorodeoxyuridine monophosphate, UFT; tegafur–uracil.

ability of 5-FU via competitive inhibition of dihydropyrimidine dehydrogenase-mediated catabolism of 5-FU. 5-FU is phosphorylated in a stepwise manner and converted into 5-fluoro-2'-deoxyuridine 5'-monophosphate which forms a ternary complex with the folate derivative 5,10-methylenetetrahydrofolate and thymidylate synthase, leading to defective DNA synthesis and repair[9]. This mechanism underlies the antitumor activity of UFT[10–13]. Conversely, cisplatin has direct cytotoxic activity, but also indirect activity via inhibition of cellular methionine influx[14]. In methionine-deficient cells, methyltetrahydrofolic acid converts homocysteine to methionine, liberating tetrahydrofolic acid, which is converted into activated 5,10-methylene-tetrahydrofolate that contributes to the ternary complex described above[9]. This mechanism is presented in Figure 1.

Several studies have demonstrated the synergistic antitumor activity of cisplatin plus 5-FU[15, 16], with particularly favorable efficacy in gastrointestinal and head and neck cancers[17, 18]. Recently, the efficacy of UFT plus cisplatin (UFT-P therapy) for CRPC has been reported[19]. The present study evaluated the safety and effectiveness of systemic UFT-P therapy for the treatment of patients with docetaxel-refractory prostate cancer.

Methods

Patients

Twenty-five patients with docetaxel-refractory prostate cancer who were treated at Nagoya City West Medical Center Johoku Hospital, Nagoya City East Medical Center Higashi City Hospital, and The Aichi Prefectural Federation of Agricultural Cooperatives for Health and Welfare Konan and Kainan Hospitals, were enrolled. These were all castrated patients who had a histologic diagnosis of prostate adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3. All patients underwent a needle biopsy of the prostate before deciding upon the initial treatment. Patients in whom serum PSA lev-

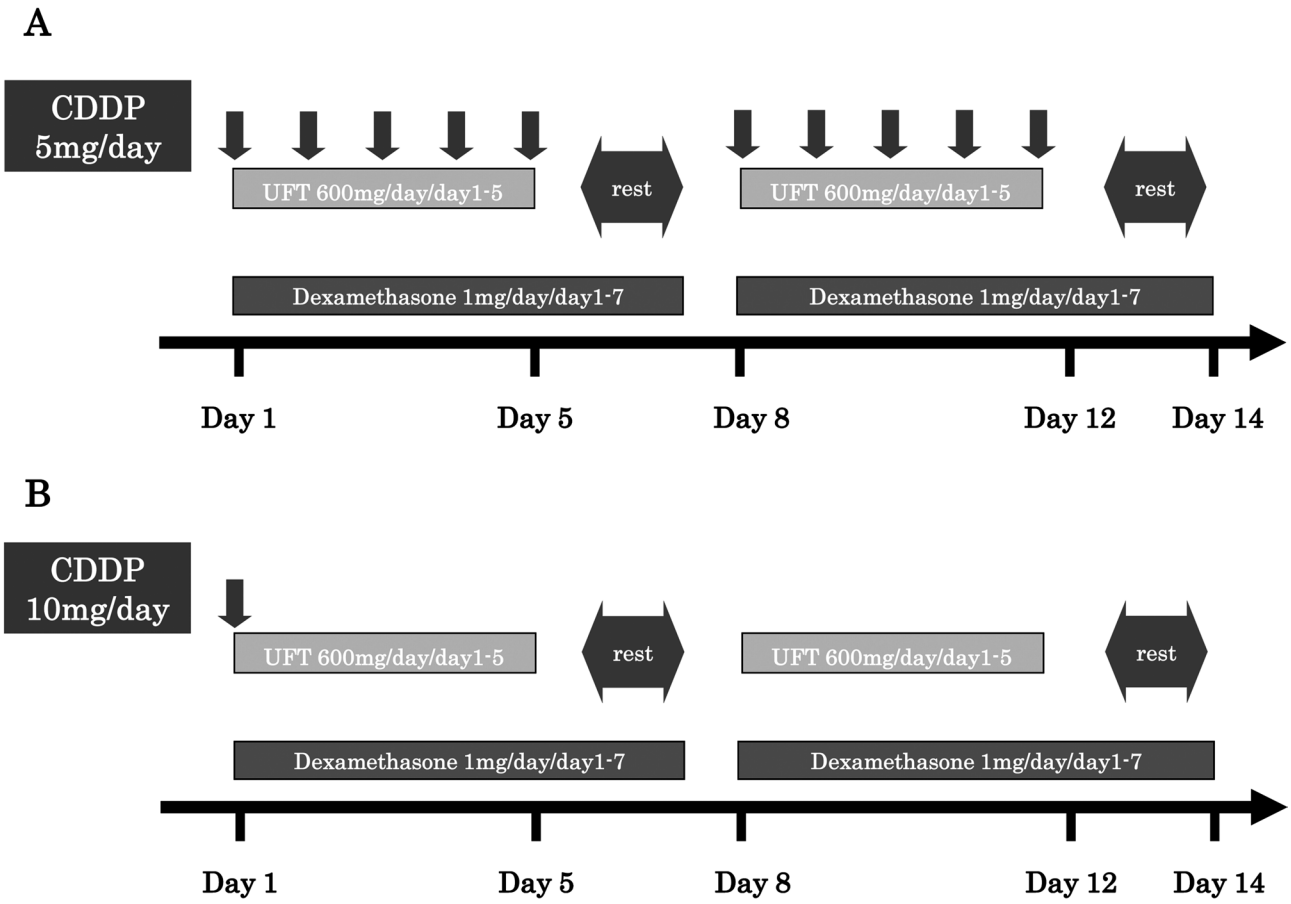

Figure 2 A: Induction therapy schedule. Intravenous cisplatin (5 mg/day) was administered 5 times a week, oral UFT (600 mg/day) was administered 5 times a week, and oral dexamethasone (1 mg/day) was administered on consecutive days. This regimen was delivered 4 times as 1 treatment cycle. B: Maintenance therapy schedule. Intravenous cisplatin (10 mg/day) was administered once every 2 weeks, oral UFT (600 mg/day) was administered 5 times a week, and oral dexamethasone (1 mg/day) was administered on consecutive days. This regimen was delivered twice as 1 treatment cycle. Treatment was continued unless serious adverse events occurred.

els increased after ADT were confirmed as not developing antiandrogen withdrawal syndrome (AWS). Patients without AWS underwent combined drug therapy (ethinylestradiol, steroids, and estramustine phosphate sodium). In this study, all these drugs were administered before docetaxel treatment. Docetaxel was administered at 75 mg/m^2 every 3 weeks (n = 8 patients) or 40 mg/patient every 2 weeks (n = 17 patients). Low-dose dexamethasone (1 mg/day) was administered in combination with docetaxel. Patients with PSA level increases over ≥ 3 consecutive measurements, despite undergoing systemic chemotherapy with docetaxel, were defined as having docetaxel-refractory prostate cancer.

Study design

Hospitalization was required for the initiation of systemic chemotherapy. A route for peripheral intravenous access was secured to facilitate drug infusion. Cisplatin (5 mg) was dissolved in physiological saline solution (500 mL) and infused intravenously for 2 hours. Oral UFT (200 mg) was administered 3 times daily with food (600 mg/day). Cisplatin and UFT were administered in cycles of 5 days per week for 3 weeks, followed by a 1-week rest period. Oral dexamethasone (1 mg/day) was continued after docetaxel therapy. After one chemotherapy cycle, serum PSA levels were measured to assess treatment response. Patients with PSA level decreases were switched to maintenance therapy, administered on an outpatient basis, consisting of oral UFT (600 mg/day) administered 5 days/week, intravenous cisplatin (10 mg/day), administered every 2 weeks, and oral dexamethasone (1 mg/day) administered on consecutive days (Figure 2). Thereafter, treatment responses according to PSA measurements were evaluated monthly.

If in-hospital treatment was not possible, patients underwent maintenance therapy on an outpatient basis, without

induction therapy. In patients with increased PSA levels, PSA doubling times (PSADTs) were calculated for the periods of 3 months prior to UFT-P therapy initiation (during treatment with docetaxel) and 3 months after UFT-P therapy initiation. Progression-free survival was defined as the period until PSA levels rose by ≥ 50%. Overall survival was defined as the duration from the date of UFT-P initiation to the date of death from any cause. In addition, median survival times from the dates of docetaxel and UFT-P therapy initiation were evaluated. All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for adverse events (version 3.0).

Statistical analyses

This study was approved by the Institutional Ethics Review Committees of all participating centers. For statistical analysis, overall survival was analyzed using JMP® software version 8 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Twenty-five patients were enrolled between January 2008 and June 2012. The patient demographic and clinical characteristics are presented in Table 1. Tumor staging revealed bone metastases in 20 patients and lymph node metastases in 7 patients.

Table 2 presents the factors representative of the response to UFT-P therapy.

Table 1 Demographic characteristics of patients

	UFT-P therapy (n = 25)
Mean age (years) (Range)	74.2 (66–88)
Mean initial PSA (ng/ml) (Range)	935.1 (1.84–9700)
Gleason	
6	1
7	5
8	6
9	11
10	2
PS	
0	8
1	8
2	4
3	5
Total prostatectomy	
Yes	2
No	23
Radiotherapy	
Yes	8
No	17
Metastatic sites at presentation	
Bone	20
Lymph node	7
Lung	2

Table 2 Factors representative of response to UFT-P therapy

	UFT-P therapy Total (n = 25)
Duration of response to ADT* (median) (Range)	23 (6–83)
Minimum PSA value after start of ADT (median) (Range)	5.8 (0.01–45)
Interval required for PSA to reach minimum value after start of ADT (median) (Range)	12.9 (3–35)
Duration of treatment with docetaxel (median) (Range)	16.6 (1–42)
Minimum PSA value after start of docetaxel (median) (Range)	28.5 (0.01–145.8)
Interval required for PSA to reach minimum value after start of docetaxel (median) (Range)	5.9 (1–21)
Total dose of docetaxel (median) (Range)	1222 (80–4700)

*UFT-P denotes UFT and cisplatin; ADT denotes androgen deprivation therapy; PSA denotes prostate-specific antigen.

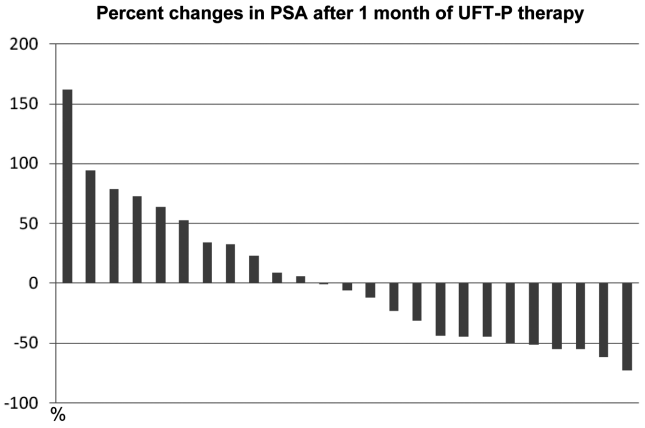

Figure 3 Each bar indicates a patient who received UFT-P therapy. The percent change in PSA levels was calculated using the following formula: ([PSA levels after 1 month of UFT-P therapy] – [PSA levels before UFT-P therapy])/PSA levels before UFT-P therapy.

Antitumor effect of UFT-P in patients with docetaxel-refractory prostate cancer

UFT-P therapy caused a decrease in PSA levels in 14 (56%) patients and an increase in PSA levels in 11 (44%; Figure 3). In those with PSA level increases, 7 of 11 patients displayed decreased PSADTs. The response rate was 84% (21/25 patients). However, upon imaging studies, UFT-P therapy was associated with a reduction in tumor volume in only one patient. In that patient, bilateral hydronephrosis due to lymph node metastasis was present before UFT-P therapy, but improved after UFT-P therapy in association with shrinkage of metastatic lymph nodes (Figure 4).

Time to PSA progression and overall survival

For those that underwent UFT-P therapy, the time to PSA progression was 6 months and the overall survival time was 14 months. The overall survival time following docetaxel plus UFT-P was 36 months (Figure 5).

Treatment-related adverse events

Overall, UFT-P therapy was well-tolerated. Adverse events included grade 1 diarrhea (20%, 5/25), anorexia (44%, 11/25), and general fatigue (100%, 25/25). There were no incidences of pancytopenia or hepatic or renal dysfunctions. No patients discontinued treatment (Table 3).

Discussion

In the present study, UFT-P therapy demonstrated substantial antitumor activity in patients with CRPC who had been administered docetaxel chemotherapy previously. In addition, treatment-related adverse events were mild and treatment discontinuation was not necessary in any patient. These findings suggest that UFT-P might be a safe and effective treatment for patients with docetaxel-refractory CRPC.

Previous studies in patients with docetaxel-refractory CRPC have indicated that cabazitaxel, MDV3100, and abiraterone were effective treatments for CRPC[20–22]. Cabazitaxel is a tubulin-binding taxane that has demonstrated antitumor activity in docetaxel-refractory cell lines[23, 24]. The TROPIC study demonstrated that cabazitaxel plus prednisone improved overall survival compared with mitoxantrone plus prednisone in patients with docetaxel-refractory CRPC. In the cabazitaxel group, the median overall survival time was 15.1 months and the median time to disease progression was 2.8 months[20]. Cabazitaxel indicated similar efficacy, in terms of survival, to UFT-P in the present study; however, the time to progression was superior in the present study (> 6 months).

MDV3100 targets multiple steps in the androgen receptor-signaling pathway. It has greater affinity for the androgen receptor, and inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment[21, 25]. The AFFIRM study revealed that patients with metastatic CRPC treated with MDV3100 had a median overall survival time of 18.4 months, and the median time to PSA progression was 8.3 months[21]. These values are similar, although slightly superior, to those presented in the present study for UFT-P therapy.

Abiraterone is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17, a critical enzyme in testosterone synthesis, thereby blocking androgen synthesis by the adrenal glands and testes and within the prostate tumor[26]. In a previous study, in patients with docetaxel-refractory CRPC treated with abiraterone, the median overall survival time was 15.8 months, and the median time to PSA progression was 8.5 months[22]. These results indicate a similar overall survival time to the present study, although the time to progression is superior. However, the definition of docetaxel-resistance in the previous study was unclear, making it difficult to compare these studies.

Overall, it appears that treatment methods for docetaxel-refractory CRPC could be divided into three drug classes: immunotherapeutics (sipuleucel-T), endocrinotherapy (MDV3100 and abiraterone), and systemic chemotherapy (cabazitaxel and UFT-P). Generally, endocrinotherapy results in few treatment-related adverse events[27]. Therefore, it might be assumed that it would be the first choice of treatment for docetaxel-refractory CRPC. However, some patients do not respond to or are ineligible for endocrinotherapy. Therefore, systemic chemotherapy might be the most appropriate for such patients.

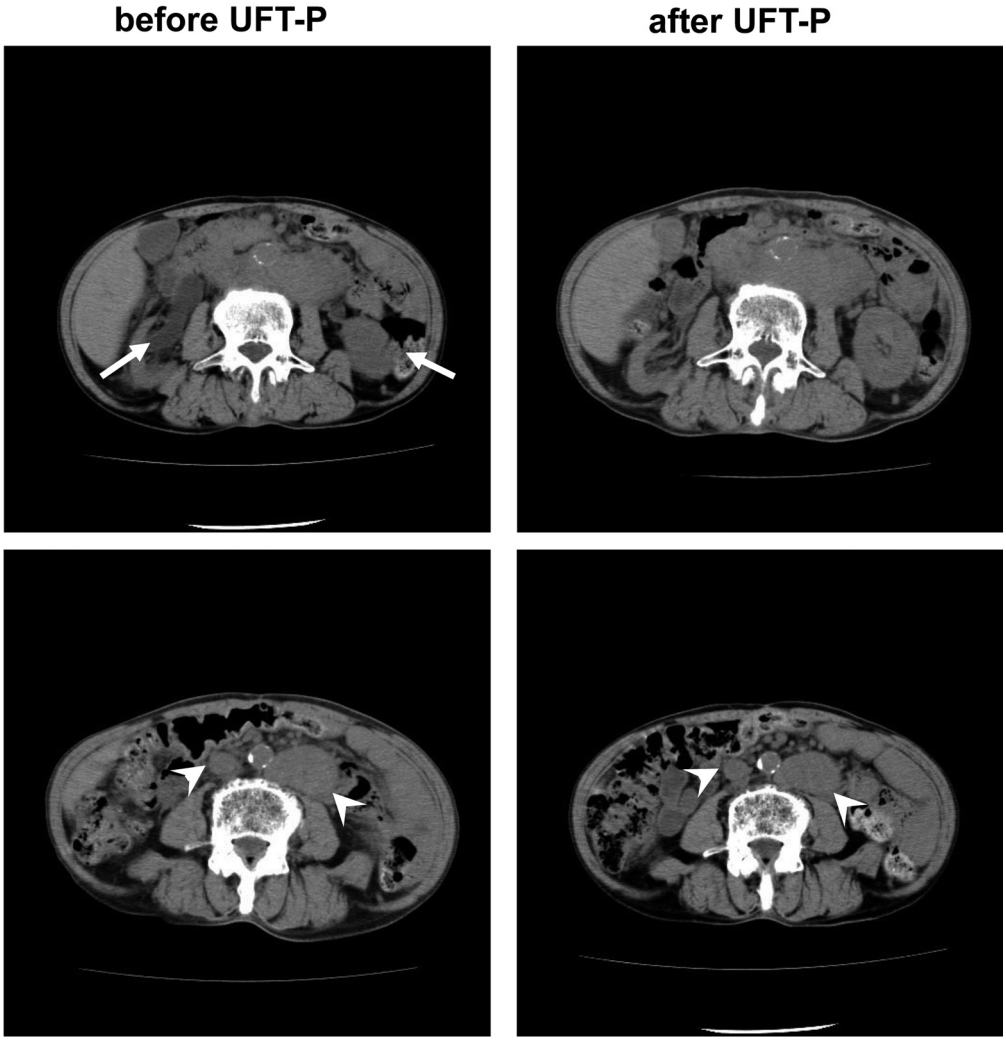

Figure 4 Computed tomography scans, indicating that bilateral hydronephrosis resolved in association with shrinkage of lymph node metastases after UFT-P therapy. The arrows indicate hydronephrosis and the arrowheads indicate lymph node metastasis.

In the present study, systemic chemotherapy with UFT-P was administered using the principles of metronomic chemotherapy. Metronomic therapy refers to the therapeutic concept of long-term, continuous exposure to anticancer drugs, with short rest periods, resembling the rhythm of a metronome[28]. High doses of anticancer drugs cannot be administered continuously on a long-term basis because of unwanted toxicity; therefore, low doses with relatively low toxicity are employed.

It was reported that the side effects of cabazitaxel occured at high frequency, although the characteristics of the anti-cancer drug were similar to docetaxel. In the TROPIC study that was conducted across 26 countries (excluding Japan), in patients with docetaxel-refractory prostate cancer, cabazitaxel was associated with a PSA response rate of 39.2% and a prolonged overall survival of 15.1 months[20]. Based on these results, cabazitaxel is now widely used in Europe and the United States. In the TROPIC study, the most common nonhematological toxicities were diarrhea, fatigue, back pain, and nausea. No grade ≥ 3 toxicities were reported; however, hematologic toxicities of neutropenia, leukopenia, anemia, and thrombocytopenia were observed, resulting in the need for growth factors administration[29]. Although the overall survival time in the present study was similar to that in the TROPIC study, the PSA response rate observed here was far superior (84%). In addition, in the present study, UFT-P therapy administered in a metronomic fashion was associated only with grade 1 diarrhea, anorex-

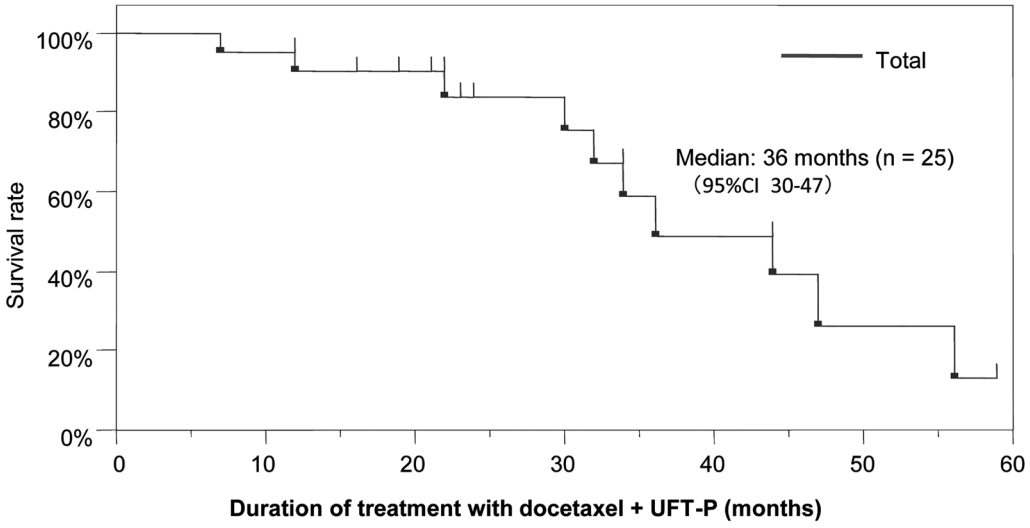

Figure 5 Overall survival after treatment with docetaxel plus UFT-P therapy.

Table 3 Adverse events

	UFT-P therapy responders (n = 21)	UFT-P therapy non-responders (n = 4)	UFT-P therapy total (n = 25)
Patients who discontinued treatment	0	0	0
Diarrhea			
Grade 1	3	2	5
Anorexia			
Grade 1	9	2	11
Pancytopenia	0	0	0
Liver/renal dysfunction	0	0	0
General fatigue			
Grade 1	21	4	25

ia, and fatigue, and additional treatments or treatment discontinuations were not necessary, suggesting the superior safety of UFT-P compared with cabazitaxel. Of note, unlike cabazitaxel, UFT-P therapy did not cause hematological toxicities.

Furthermore, in the present study, UFT-P therapy was based on the idea of biochemical modulation. Previous studies in patients with prostate cancer have reported response rates of UFT alone or cisplatin alone as 18.2% and 19%, respectively[10, 30]. In the present study, strong anticancer effects were noted using these treatments in combination. In a previous study investigating combination therapy of UFT plus cisplatin for CRPC patients, the median overall survival time was 19 months, and the median time to PSA progression was 11 months[19]. Our study demonstrated for the first time the efficacy of UFT plus cisplatin for docetaxel-refractory CRPC.

In conclusion, UFT-P therapy is a safe and effective regimen for the treatment of docetaxel-refractory CRPC. In addition, because CRPC occurs largely in elderly men, the low-dose nature of the metronomic UFT-P regimen would be especially useful and could be administered continuously. Because the present study was small, large-scale studies with longer follow-up are required.

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