Phase II Trial of Oral Uracil/Tegafur Plus Leucovorin in Patients with Hormone-Refractory Prostate Carcinoma

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BACKGROUND. The current study evaluated the efficacy of oral uracil/tegafur (UFT) and leucovorin (LV) in patients with hormone-refractory metastatic prostrate carcinoma.

METHODS. Twenty-eight patients with hormone-refractory metastatic carcinoma of the prostate who had undergone antiandrogen withdrawal and no more than 1 prior chemotherapy treatment were enrolled on a single-institution Phase II trial. Patients were treated with oral UFT at a dose of 300 mg/m^2/d and oral LV at a dose of 90 mg/day for 28 days followed by 7 days off therapy on a 35-day cycle regimen.

RESULTS. Twenty-six patients were evaluable for response and toxicity. There was no response by objective criteria in 9 patients with measurable disease. Four responses by prostate-specific antigen (PSA) criteria (i.e., PSA decrease by $>$ 50%) were noted (15%) lasting a mean of 20.5 weeks. Therapy was generally well tolerated, with 2 patients developing Grade 4 toxicity (1 patient each with diarrhea and hand-foot syndrome) and 4 patients having significant Grade 3 toxicity (anemia, hyperbilirubinemia, and vomiting) (Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria). Six patients had stable disease by clinical, laboratory, and radiologic criteria for an average of 5 cycles of treatment (25 wks).

CONCLUSIONS. Although UFT and LV are generally well tolerated in the setting of hormone-refractory metastatic prostate carcinoma, the combination has a low level of activity. Its toxicity and activity is similar to that observed when intravenous 5-fluorouracil or capecitabine are given alone. It may be an option for further investigations in combination regimens. ***Cancer* 2006;106:1715–21.**

KEYWORDS: prostate carcinoma, chemotherapy, fluoropyrimidines, hormone refractory.

Metastatic hormone-refractory adenocarcinoma of the prostate remains a major cause of morbidity in American men. It is the second leading cause of male cancer deaths, with 40,000 men dying of the disease each year.[1] Unlike local disease, which has a 100% 5-year survival rate, the relative survival rate at 5 years for patients with distant disease at diagnosis is estimated to be 32%. For patients with metastatic disease, the goals of therapy include prolonging survival, providing palliation, decreasing tumor burden, and improving quality of life. Despite being noncurative, hormonal therapy has been the mainstay of therapy, with high efficacy (78-80%) and relatively low morbidity. After a response to androgen ablation, nearly 50% of patients with advanced prostate carcinoma will experience tumor progression within 2 years. The median survival for patients with

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progressive disease is 12 months to 18 months. Objective response rates to secondary hormonal manipulation are usually $\leq$ 20%.[2] Options for further therapy in this setting include chemotherapy or investigational trials. Although docetaxel has recently been shown to prolong survival in this stage of androgen-independent prostate carcinoma by 2 months to 3 months in Phase III trials,[3,4] the toxicities are significant. Therefore, docetaxel may not be the preferred option to treat elderly patients and/or those patients with limited hematologic reserves.

Several studies using 5-fluorouracil (5-FU) have been performed in patients with hormone-refractory prostate carcinoma (HRPC). In 1973, in what to our knowledge was the first multicenter, randomized trial comparing chemotherapy with standard treatment performed by the National Prostatic Cancer Project[5] 125 patients with metastatic disease were randomized to receive either conventional hormonal versus chemotherapy with 5-FU or cyclophosphamide. Both agents outperformed the standard treatment arm in terms of subjective response parameters, objective measures such as reduction in primary tumor response (6% standard vs. 29% 5-FU vs. 31% cyclophosphamide), and survival.

Subsequent Phase II trials for advanced HRPC using 5-FU monotherapy demonstrated modest activity. Objective response rates ranged from a prostate-specific antigen (PSA) response rate of 12% to a response rate of $>$ 20% for measurable disease, with significant toxicity reported.[6–9] Continuous infusion of 5-FU resulted in similar response rates but more manageable toxicity.[10,11] Subjective measures including improvement of pain and objective improvement in performance status were observed in approximately 36% of patients. The addition of intravenous (i.v.) leucovorin or interferon did not augment response in this population.[12–14]

Tegafur, a 5-FU precursor, has shown activity in several malignancies when administered i.v. or orally in animal models.[15] A prodrug of 5-FU, tegafur is hydroxylated and converted to 5-FU by hepatic microsomal enzymes and may lead to sustained levels of 5-FU in tumor-specific tissues.[16] Studies have suggested that the clinical activity of tegafur may be attributable to the slow release of 5-FU. Uracil inhibits the activity of hepatic dihydropyrimidine dehydrogenase, an enzyme involved in 5-FU catabolism, thereby leading to increased 5-FU levels when tegafur is administered with uracil.[17] Levels of 5-FU in tumor were found to be higher after the administration of tegafur and uracil than after administration of tegafur alone; 5-FU levels in tumor decreased slowly, whereas levels in plasma decreased rapidly. Coadministration of different molar ratios of tegafur and uracil has been examined in tumor-bearing rats. The highest tumor tissue: blood partition coefficient was noted with a uracil:tegafur molar ratio of 4:1.[18]

Early clinical development of tegafur in the U.S. had been delayed due to a narrow dose-toxicity relation with severe gastrointestinal and central nervous system toxicity.[19–21] However, clinical trials in Japan using oral, divided-dose schedules demonstrated modest clinical efficacy but only mild toxic effects in patients with malignant tumors, including colorectal, gastric, breast, and head and neck cancers.[22] This stimulated a renewed interest in the combination of uracil and tegafur (UFT) in the U.S. Pharmacokinetic studies of UFT measuring tegafur, uracil, and 5-FU were performed and confirmed the dose-limiting toxicities noted earlier. These studies noted that the toxicities appeared to correlate with 5-FU clearance and that there was wide interpatient variability.[23]

As with 5-FU, leucovorin potentiates the antitumor effects of tegafur.[24] Phase I and II trials with UFT plus oral leucovorin demonstrated an enhanced response in terms of the antineoplastic effects of UFT, with no major increase in toxicity noted in patients with metastatic colorectal carcinoma.[25,26] Subsequently, a large Phase III trial of adjuvant therapy for 1530 patients with resected colon carcinoma conducted by the National Surgical Adjuvant Breast and Bowel Project compared the combination of UFT with calcium folinate versus 5-FU with calcium folinate and found very comparable toxicity among the 2 regimens, with a trend toward fewer Grade 3 and 4 gastrointestinal and mucosal effects, neutropenia, and fatigue with the UFT/leucovorin regimen.[27]

Patients have been shown to prefer oral therapy as long as efficacy is not sacrificed[28] and encouraging results in adjuvant treatment of adenocarcinoma of the lung with UFT revived interest in this agent among U.S. oncologists.[29] Based on these results, we conducted a Phase II trial of UFT and leucovorin in men with HRPC to better characterize the activity of this drug combination in this disease setting.

MATERIALS AND METHODS

Patients

Eligible patients were required to have histologically proven adenocarcinoma of the prostate with progressive disease after orchiectomy or androgen ablation and antiandrogen withdrawal. Disease progression was defined as an increase in measurable disease, the development of new lesions on bone scan (or other imaging study), or rising PSA levels $>$ 50% over the nadir value. Levels were measured on 2 separate oc-

casions, at least 4 weeks apart, with the second PSA drawn at least 4 weeks after antiandrogen withdrawal.

Patients age ≥18 years were required to have a performance status of 0 to 2 on the Zubrod scale. Adequate hematologic reserve (absolute neutrophil count ≥1500/mm^3 and platelet count ≥100,000/mm^3), hepatic (total bilirubin ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase < 2 times the upper limits of normal) and renal function (creatinine ≤1.5 times the upper limits of normal) were required for study entry.

Patients who received no more than 1 prior chemotherapy regimen were eligible if previous therapy was completed at least 3 weeks before the study entry date. Patients were required to have recovered from any recent surgical procedure (interval of 3 weeks) and be able to swallow UFT capsules and leucovorin tablets. Patients who had a previous malignancy, except those who had been free of disease for > 5 years or those with appropriately treated nonmelanoma skin cancer or superficial transition cell carcinoma of the bladder were excluded. Those with serious, concurrent, uncontrolled medical disorders (cardiovascular, hepatic, hematologic, renal pulmonary, or psychiatric) or febrile illness at the time of study entry were also excluded. The study protocol and consent document were reviewed and approved by the University of Michigan Institutional Review Board. All patients provided written informed consent in accordance with federal, state, and institutional guidelines.

Evaluations

Pretreatment evaluation consisted of a history and physical examination with assessment of performance status and laboratory studies, including complete blood count, serum chemistry profile, PSA level, radionuclide bone scan, computed topography of the abdomen and pelvis, electrocardiogram, and chest radiograph. Complete blood counts, including differential and platelet counts, were monitored weekly and chemistry profiles were repeated every 3 weeks. Physical examination and symptom assessment was completed after each 35-day cycle. PSA levels were obtained on the start of each cycle. Imaging studies were repeated every 2 cycles (or 10 wks) if positive at baseline.

Treatment Regimen

All therapy in this study was administered in the outpatient setting. UFT and leucovorin were provided by Bristol-Myers Squibb Pharmaceutical Research Institute (Wallingford, CT). Treatment consisted of oral UFT with a daily dose of 300 mg/m^2 divided into 3 separate doses administered every 8 hours. The UFT dose was rounded to the nearest 100 mg. Leucovorin at a dose of 30 mg was given orally concurrent with UFT for a total daily dose of 90 mg/day. Patients were instructed to take 4-8 ounces of water with their medications and not to consume food for 1 hour before or after ingestion of the medication. The drug was administered for 28 days followed by a 7-day period off treatment to allow adequate recovery from toxicity (Fig. 1). Antiemetic therapy was given as needed. Treatment continued until significant toxicity or disease progression occurred. Maintenance of primary androgen suppression using a gonadotropin-releasing hormone (GnRH) agonist in patients who had not undergone prior orchiectomy was required throughout the duration of the study.

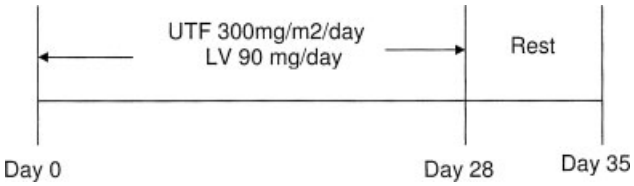

FIGURE 1. Treatment schedule.

All subsequent cycles of therapy required that toxicity resulting from the prior cycles had resolved and that hematologic parameters had recovered to meet the entry criteria. Dose modification of UFT was based on the highest grade of toxicity observed during the previous cycle or the occurrence febrile neutropenia. If bone marrow suppression was present on Day 36, treatment was delayed until resolution of toxicity and resumed with the UFT dose adjusted according to the highest toxicity observed in the previous cycle. If the highest grade was Grade 0-2, treatment was at the same dose level. If the highest toxicity was Grade 3-4, the next cycle was decreased by 1 dose level (50 mg/m^2/day) Once decreased due to toxicity, the dose level was maintained and not increased for subsequent cycles. Leucovorin was withheld if UFT was not given. No change in dosing for leucovorin was made. Treatment was discontinued in any patients who required more than a 2-week delay before retreatment or in patients who required a dose reduction below Level −3 (ie, −1 indicates 250 mg/m^2/day, −2 indicates 200 mg/m^2/day, and −3 indicates 150 mg/m^2/day).

Toxicity and Response Criteria

Toxicity was graded according to the revised National Cancer Institute Common Toxicity Criteria. Response was assessed using standard criteria for measurable disease, if present. In the case of elevations in serum PSA or bone-only disease, complete response required

the disappearance of all measurable and nonmeasurable but assessable lesions with a decrease in serum PSA to < 1.0 ng/mL for at least 4 weeks. A partial response was defined as a > 50% decrease in any measurable lesions and/or a 50% decrease in serum PSA without worsening of disease-related symptoms. Disease progression was defined as the appearance of new signs and symptoms of metastatic disease, new lesions on imaging studies, or an increase in the PSA of 50% over baseline or nadir values, or a 25% increase in the size of any measurable lesion. All patients not meeting these definitions were considered to have stable disease.

Statistical Considerations

The trial had a 2-stage Gehan optimized design with a sample size of 25 patients to estimate the PSA response rate with a standard error of < 0.10. If the treatment had a PSA response rate of < 20%, then the drug would not be considered worth being tested in a Phase III trial. The trial was designed to be stopped if there were no PSA responses noted among the first 14 patients. Because 3 PSA responses were noted in Stage I with 14 patients evaluated, the trial continued beyond the initial 14 patients to a total of 26 evaluable patients.

RESULTS

Characteristics of the Patients

Twenty-eight patients were entered in the current study from our institution; 26 were treated and evaluable for response and 2 were ineligible (after enrollment, 1 patient was discovered to have had a prior colorectal malignancy and the other patient withdrew after enrollment secondary to a decrease in his PSA). The characteristics of this patient population are typical of patients receiving chemotherapy for HRPC (Table 1). The median age was 68 years (range, 42-81 yrs; 19% were age < 65 yrs and 81% were age ≥ 65 yrs) and generally had a good performance status (61% were asymptomatic and the remaining patients had a performance status of either 1 or 2). All patients had documented progressive disease (rising PSA level and/or new or growing metastases) while undergoing continued androgen ablation and after at least 1 antiandrogen withdrawal maneuver. Nine patients underwent prior radical prostatectomy, 5 received prior radiation therapy to the prostate as their primary treatment (2 with adjuvant androgen ablation), and 12 patients received systemic hormonal therapy as primary treatment. At the time of disease progression, all patients had received prior hormonal therapy, with a treatment distribution that included leuprolide (69%), goserelin (31%), bicalutamide (54%), flutamide (38%), diethylstilbestrol (38%), prednisone (31%), and ketoconazole (15%). An average of 2.6 hormonal maneuvers were undertaken per patient, including a withdrawal maneuver for all the patients before systemic cytotoxic chemotherapy. Eleven patients (42%) had prior chemotherapy predominantly consisting of multiple regimens, with the most common being a combination of etoposide, estramustine, and paclitaxel (8 patients) and 3 patients received prior treatment with mitoxantrone and prednisone.

TABLE 1
Patient Characteristics

		No. of patients
Enrolled/evaluable		28/26
Age, y	Median	68
	Range	42-81
Race	White	23
	African American	3
Performance status (ECOG)	0	16
	1	9
	2	1
Prior therapy	Prostatectomy	9
	Radiation	17
	Hormones	26
	Chemotherapy	11
PSA at entry in ng/mL	Mean	55
	Range	4-2351
Extent of disease	Bone	22
	Lymph node	6
	Soft tissue	4
	Liver	2

ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen.

The majority of patients (85%) had bone metastases. Nine patients had visceral disease, including 6 patients with pelvic and/or abdominal lymphadenopathy; 4 patients had soft tissue metastasis and 2 patients had liver metastases (Table 1).

Patients were treated from 1 to a maximum of 8 35-day cycles, with the majority of patients (17 patients) completing at least 2 cycles of therapy. A total of 138 cycles of treatment were delivered and the majority of patients were able to finish 2 cycles of therapy. Treatment was generally well tolerated and only 13 treatment cycles (10%) required dose reductions due to diarrhea, hand-foot syndrome, hyperbilirubinemia, or a Grade 3 hematologic toxicity (anemia).

The most common treatment-related adverse events are summarized in Table 2. These included thrombocytopenia, anemia, neutropenia, and diarrhea. One patient presented during Cycle 4 with Grade 4 hand-foot syndrome, which progressed acutely from Grade 1 during his prior cycle. Treatment in this pa-

TABLE 2
Toxicities

	Grade*		
Toxicity	**2 (%)**	**3 (%)**	**4 (%)**
Hematologic			
Anemia	9 (34)	2 (8)	—
Thrombocytopenia	20 (77)	—	—
Neutropenia	10 (38)	—	—
Nonhematologic			
Hyperbilirubinemia	4 (15)	1 (4)	—
Diarrhea	4 (15)	2 (8)	1 (4)
Nausea	2 (8)	—	—
Emesis	—	1 (4)	—
Hand-foot syndrome	—	—	1 (4)

* Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

tient and for 2 others was discontinued due to diarrhea and nausea/emesis. In the majority of patients, treatment was discontinued due to disease progression. There were no febrile neutropenic episodes or deaths reported during this trial.

PSA response according to standardized criteria were noted in 4 patients (15%, 95% confidence interval, 9-21%). Response durations in these 4 patients were 14 weeks, 17 weeks, 18 weeks, and 33 weeks, respectively, with a mean duration of response of 20.5 weeks. Minor reductions in PSA ($>$ 20% but $<$ 50%) were noted in 2 additional patients. The median time to tumor progression (including PSA progression) for the 17 patients completing at least 2 cycles of treatment was 7 weeks. There were no responses noted among 9 patients with objective measurable disease.

DISCUSSION

Patients with advanced, HRPC can present a difficult management problem. Response to secondary hormonal manipulations are reported to be relatively low and of brief duration.[2] Therefore, various cytotoxic chemotherapeutic agents have been evaluated in this patient population. Mitoxantrone in combination with a steroid (prednisone or hydrocortisone) received approval from the U.S. Food and Drug Administration (FDA) in the late 1990s based on a Canadian and a U.S. Cancer and Leukemia Group B (CALGB) trial demonstrating palliative benefits that were durable.[30,31] However, response rates with mitoxantrone are reported to be low (approximately in the 10% range in combination with prednisone) and typical anthracycline cardiac toxicity limit continued and prolong use. Various other chemotherapeutic agents including alkylating agents such as cyclophosphamide,[32] newer anthracyclines such as epirubicin,[33,34] and taxanes such as paclitaxel[35,36] also have been found to result in low response rates in the 9% to 46% range. Recently, docetaxel has been shown to have a substantially higher PSA response (45-50%) and objective response rate (17%) in the 2 definitive Phase III trials that led to its approval by the FDA on a every-3-week basis due to a prolongation in survival of approximately 2 months to 3 months.[3,4] However, significant hematologic toxicity in up to 54% of treated cycles limits its use for many elderly and marginal performance patients. Therefore, there remains a need to explore additional active agents in adenocarcinoma of the prostate.

Experience with 5-FU in patients with HRPC has been mixed, with no responses noted in Phase II trials with 5-FU and leucovorin given as bolus injections or continuous infusion over 5 days.[11,13] However, 5-FU given as a continuous infusion of 300 mg/m^2 did demonstrate a significant palliative effect.[10]

In this Phase II trial of UFT with leucovorin in patients with HRPC, the regimen has shown a confirmed PSA response rate of 15% (4 of 26 patients) with a mean duration of response of 20.5 weeks (14 weeks, 17 weeks, 18 weeks, and 33 weeks, respectively). In addition, 2 minor PSA responses also were observed. It is interesting to note that very similar efficacy results for another oral prodrug formulation of 5-FU, capecitabine, also was reported by Swiss investigators in HRPC patients.[37] In this Phase II trial with 25 patients, a PSA response of 12% and mean duration of response of 20 weeks was obtained; in addition, no objective responses were noted with capecitabine. This close correlation of disease activity noted in both oral prodrug formulations of 5-FU validates to some extent the conclusion that these agents have minimal activity in HPRC. Although hematologic toxicities including Grade 2 thrombocytopenia (77%), anemia (42%), and neutropenia (38%) were the major adverse effects observed for patients treated with the combination of UFT and leucovorin, nonhematologic toxicities such as hand-foot syndrome (32%), nausea (32%), and diarrhea (16%) were the major toxicities observed with the use of capecitabine in HRPC patients.

The large adjuvant trial undertaken in Japan for the postsurgical adjuvant treatment of patients with Stage I adenocarcinoma of the lung using UFT for 2 years reported no Grade 4 toxicities and limited ($<$ 1%) Grade 3 toxicities in terms of nausea, emesis, diarrhea, and increase in aspartate aminotransferase.[38] The toxicity rates observed during this study in patients with HRPC were higher compared with those reported in the Japanese adjuvant trial, possibly due to a higher UFT dose (300 mg/m^2/day compared with

250 mg/m^2/day) and a population that was older and at a more advanced stage of disease.

Treatment with UFT and leucovorin was shown to be minimally active for patients with HRPC. It is interesting to note that the activity observed with this prodrug of 5-FU is very close to that noted with another prodrug, capecitabine, and both paralleled the activity reported for infusional 5-FU in HRPC. Although the oral equivalents of 5-FU were generally well tolerated, there were significant side effects of treatment, including reversible cytopenias, diarrhea, and hand-foot syndrome that required regular monitoring by an oncologist. Given this minimal activity, we do not recommend further clinical investigations of the single-agent treatment of patients with HRPC with these agents. However, combinations of this regimen, given its oral route and ease of administration along with acceptable tolerance, may be an option in combination with other cytotoxic agents such as docetaxel or newer biologic agents if the synergy for their action is demonstrated in preclinical models.

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