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High-dose oral tegafur-uracil maintenance therapy in patients with uterine cervical cancer

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Objective: The aim of this study was to determine the efficacy and toxicity of oral administration of tegafur-uracil (UFT) at a high dose, 600 mg/day, based on the tegafur dose, against uterine cervical cancer.

Methods: This study consisted of a retrospective analysis. From April 1986 to March 1997, 309 patients with uterine cervical cancer were registered. Oral UFT was administered to 162 patients for maintenance therapy after an initial treatment (the UFT group). The other 147 patients were not treated with UFT (the control group). The survival rate was calculated for both groups and statistically analyzed using the log-rank test. Adverse events were compared between the UFT and control groups.

Results: In the UFT group, 103 patients (63.6%) received UFT for ≥90 days. The drug dose was 600 mg/day for 137 patients (84.6%) and 300 to 400 mg/day for the remainder. The overall survival rate was significantly higher in the UFT group than in the control group ($p<0.05$). The prognosis was particularly favorable in stage III cases, in cases of squamous cell carcinoma, and in cases that were treated by radiotherapy. The most frequent side effects were nausea/vomiting (12.2%), appetite loss (10.1%), and leukopenia/neutropenia (5.8%).

Conclusion: High-dose oral UFT maintenance treatment prolonged the disease-free survival and overall survival of patients with uterine cervical cancer, particularly of those with advanced disease.

Keywords: Follow-up Studies; Maintenance Chemotherapy; Survival Rate; Tegafur; Uterine Cervical Neoplasms

INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide. There are approximately 530,000 new cases and 275,000 associated deaths each year [1]. In advanced uterine cervical cancer, the addition of chemotherapy to external pelvic radiation has been proposed because systemic chemotherapy further enhances local control and improves the overall survival. The main agents are cisplatin and 5-flurouracil (5-FU), concurrent chemoradiotherapy with either weekly cisplatin or monthly cisplatin and 5-FU are recommended for patients with advanced uterine cervical cancer. Oral 5-FU is also a mainstay in the maintenance therapy for cervical cancer in most cases in Japan. Among 5-FU derivative chemotherapeutic agents, tegafur-uracil (UFT) is an oral antineoplastic drug consisting of tegafur and uracil in a fixed 1:4 molar ratio. Tegafur is an oral prodrug of 5-FU and is slowly metabolized by cytochrome P450 to 5-FU [2-4]. Uracil competitively inhibits

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dihydropyrimidine dehydrogenase (DPD), which results in increased and sustained plasma and tumor 5-FU concentrations. The 5-FU that results from the metabolism of tegafur is modulated by formyltetrahydrofolic acid (folic acid). More recently, studies that have compared adjuvant chemotherapy with UFT after surgery and surgery alone have been reported and clearly proved a survival benefit of adjuvant UFT treatment for lung, gastric, colorectal, and breast cancer [5-11]. In early-stage uterine cervical cancer, oral 5-FU after surgery with radiotherapy appears to be useful for patients who have some risk factors but not for those with pelvic lymph node metastases [12]. However, the extent of impact of adjuvant treatment with oral UFT on patients with advanced cervical cancer remains unclear. Although the amount of UFT per day was high in the above-described trial, it was standardized at 300 to 400 mg/day for adjuvant therapy of advanced cervical cancer. It remains unclear whether the high dose of this oral compound will become tolerable with infrequent observation of toxic effects and result in a significant improvement in the survival rate.

This study was conducted to determine the efficacy and toxicity of adjuvant and maintenance therapy with oral administration of UFT at a high dose, 600 mg/day, based on the tegafur dose, against uterine cervical cancer.

MATERIALS AND METHODS

1. Study design

This retrospective study was planned in a total of five institutions in Kumamoto, Japan. In these five institutions, between April 1986 and March 1997, patients with advanced cervical cancer were enrolled. The patients were required to meet the following criteria: histologically confirmed primary uterine cervical carcinoma; International Federation of Gynecology and Obstetrics (1988 FIGO) stages Ib to IV; performance status of 0 to 2; adequate bone marrow, renal, and hepatic function as evidenced by a white blood cell count >3,000 cells/μL, platelet count >100,000 cells/μL, serum creatinine level <2.0 mg/dL, blood urea nitrogen (BUN) level <30 mg/dL, serum bilirubin level <1.5 mg/dL, and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <2 times the normal limit; and no serious complicated illness such as renal hepatic, cardiac, or pulmonary disease. Patients also could not have previously received any biochemical modulation.

In total, 309 patients with advanced cervical cancer were allocated to either the UFT-treated group (the UFT group) or the UFT-untreated group (the control group). The study group consisted of 162 selected consecutive patients with advanced cervical cancer who were enrolled in this study at five institutions in Kumamoto between August 1992 and March 1997. The patients were treated by oral administration of UFT at a dose of 600 mg/day for maintenance therapy after an initial treatment. A group of 147 similar patients who had received the same treatment in five institutions in Kumamoto between December 1986 and March 1997 was used as an external control group. These patients were required to meet the criteria mentioned above and not treated with UFT. In the UFT and control groups, 43 patients (26.5%) and 41 patients (27.9%) received radical hysterectomy combined with pelvic lymph node dissection; 58 (35.8%) and 65 (44.2%) received radiotherapy; 26 (16.0%) and 29 (19.7%) received radiotherapy and radical surgery; and 14 (8.6%) and six (4.1%) received a combination of surgery, radiotherapy, and chemotherapy, respectively. Postoperative pelvic radiotherapy was advocated for patients with pelvic lymph node metastasis, deep stromal invasion, and parametrial invasion. Toxicity was recorded by grade according to the National Cancer Institute Common Toxicity Criteria ver. 2.0. Monthly complete blood counts,

Table 1. Patient characteristics and treatment

Characteristic	Control group (n=147)	UFT group (n=162)
Median age (yr)	62.0±14.1	61.0±14.1
FIGO stage		
I	58 (39.5)	64 (39.5)
II	37 (25.2)	42 (25.9)
III	40 (27.2)	39 (24.1)
IV	12 (8.1)	17 (10.5)
Histologic type		
Squamous cell carcinoma	134 (91.2)	133 (82.1)
Adenocarcinoma	9 (6.1)	17 (10.5)
Adenosquamous carcinoma	4 (2.7)	6 (3.7)
Undifferentated carcinoma	0	1 (0.6)
Others	0	5 (3.1)
Primary treatment		
RT alone	65 (44.2)	58 (35.8)
Surgery alone	41 (27.9)	43 (26.5)
Surgery/RT	29 (19.7)	26 (16.0)
Surgery/RT/chemotherapy	6 (4.1)	14 (8.6)
RT/chemotherapy	4 (2.7)	11 (6.8)
Surgery/chemotherapy	2 (1.4)	10 (6.3)

Values are presented as mean±SD or number (%). Chemotherapy means cispatin based therapy, not included the oral administration of UFT. Chemotherapy regimens were given to patients before the oral administration of UFT.
FIGO, International Federation of Gynecology and Obstetrics; RT, radiotherapy; UFT, tegafur-uracil.

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including white blood cell, red blood cell, and platelet counts, were performed to assess myelosuppression. A complete chemistry panel, including serum creatinine, BUN, bilirubin, AST, and ALT levels, was also obtained. The UFT treatment was continued for up to 2 years until side effects became intolerable. In some cases, the dose was reduced from 600 mg/day to 300 to 400 mg/day when side effects were beyond control. Severe (grade 3/4) toxicity related to chemotherapy resulted in dose reduction.

2. Statistical analysis

Survival was estimated as the time of study entry until death as a result of any cancer. Progression-free survival was defined as the time from study entry to the initial observation of disease progression or death as a result of any cancer. The survival rate was statistically analyzed using the log-rank test. No patients were lost to follow-up in this study. Each patient was followed until death or is alive with the disease status being known. This study was approved by the Institutional

Table 2. Efficacy of UFT in the patients with cervical cancer

Variable	Overall survival (%)			Disease-free survival (%)		
	Control group	UFT group	p-value	Control group	UFT group	p-value
All patients	60.8	73.8	0.049	59.8	68.5	0.076
FIGO stage						
I	88.9	91.5	0.665	89.2	91.6	0.661
II	46.7	71.3	0.644	61.6	71.6	0.855
III	34.9	62.1	0.012	38.3	62.5	0.026
IV	20.8	35.3	0.318	10.4	37.6	0.204
Histologic type						
Squamous cell carcinoma	60.7	74.1	0.062	64.6	75.2	0.083
Adenocarcinoma	85.7	80.6	0.764	85.7	80.8	0.694
Adenosquamous carcinoma	25	62.5	0.29	25	62.5	0.242
Primary treatment						
Radiotherapy alone	48.7	64.3	0.068	48.9	65.6	0.082
Surgery alone	94.7	92.7	0.746	94.9	92.7	0.701
Surgery/radiotherapy	53.5	82.7	0.193	59.5	83.2	0.093

The effect of UFT administration on overall survival rate was analyzed according to FIGO staging, histological type, and primary treatment. A p-value between patients with and without UFT administration.
FIGO, International Federation of Gynecology and Obstetrics; RT, radiotherapy; UFT, tegafur-uracil.

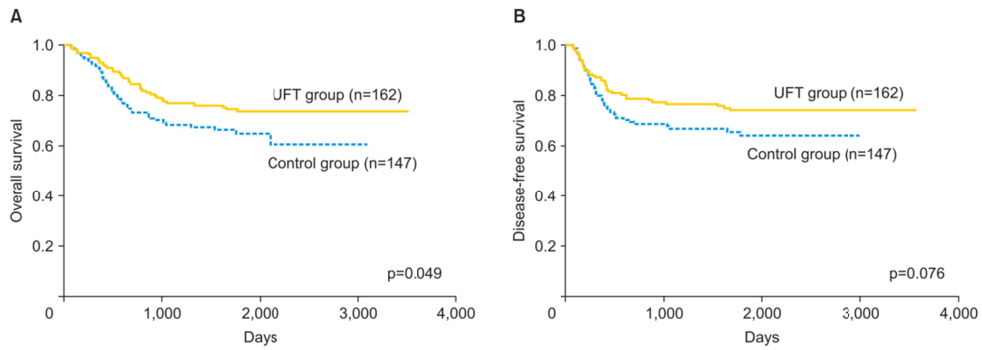

Fig. 1. Survival curves among 309 patients with uterine cervical cancer in the tegafur-uracil (UFT) and the control group. Kaplan-Meier estimates of (A) the overall survival (p=0.049), (B) the disease-free survival (p=0.076).

Table 3. Efficacy of long-term oral administration of UFT in the patients with cervical cancer

Variable	Overall survival (%)			Disease-free survival (%)		
	Administration period <90 days	Administration period ≥90 days	p-value	Administration period <90 days	Administration period ≥90 days	p-value
All patients	59.6	81.4	0.001	62.2	81.4	0.001
FIGO stage						
I	84.4	94.9	0.13	84.4	94.9	0.134
II	54.8	79.8	0.072	58.7	79.3	0.063
III	55.3	66.8	0.334	61.1	64.8	0.467
IV	17.1	57.1	0.001	17.1	60	<0.001
Histologic type						
Squamous cell carcinoma	59.6	81	0.003	62.2	81	0.003
Adenocarcinoma	71.4	87.5	0.416	71.4	87.5	0.361
Adenosquamous carcinoma	66.7	50	0.081	66.7	66.7	0.715
Primary treatment						
Radiotherapy alone	44.7	74.9	0.01	49.1	75.3	0.006
Surgery alone	88.9	93.6	0.594	88.9	93.5	0.594
Surgery/radiotherapy	87.5	80.4	0.759	88.9	80.8	0.761

We compared the disease free survival rate in the patients who received the drug for ≥90 days with those who received the drug for <90 days. A p-value between patients received the drug for 90 days or more, and for less than 90 days.
UFT, tegafur-uracil; FIGO, International Federation of Gynecology and Obstetrics.

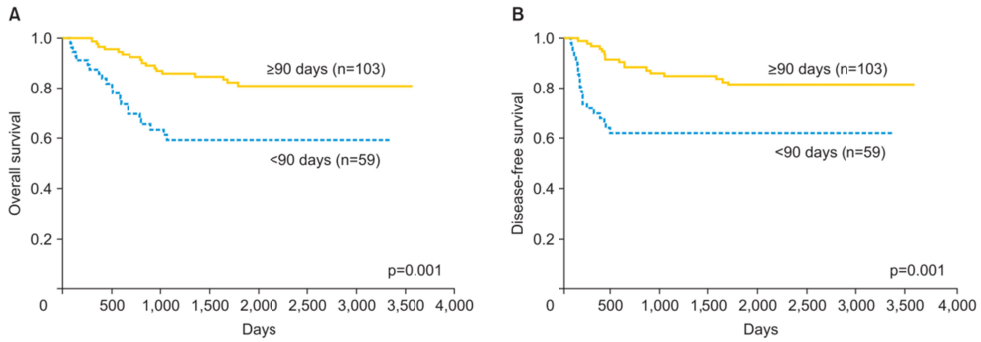

Fig. 2. Survival curves of the tegafur-uracil (UFT)-treated patients between those who received the drug for ≥90 days and <90 days. Kaplan-Meier estimates of (A) the overall survival (p=0.001), (B) disease-free survival (p=0.001).

Review Board of Kumamoto University (Japan).

RESULTS

The patient characteristics of the two groups are listed in **Table 1**. The median follow-up period was 52 months (range, 1 to 119 months). The patient characteristics, including background factors such as age, FIGO stage, histological type, and therapeutic modality, were well balanced between the UFT and control groups. In the UFT group, 108 patients (63.5%) received UFT for ≥90 days, and the average duration was 217.2 days. The average total dose was 120.2 g (range, 1.0 to 544.0 g).

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1. Response, survival, and disease-free survival

The overall survival rate was significantly higher in the UFT group (73.8%) than in the control group (60.8%; p<0.05) (**Table 2**, **Fig. 1A**). Next, the effect of UFT administration on survival was analyzed according to FIGO staging, histological type, and primary treatment (**Table 2**).

There was a significant difference in survival between the UFT group and the control group among the stage III patients (UFT group, 62.1%; control group, 34.9%; p=0.012) (**Table 2**, **Supplementary Fig. 1A**). Among the patients with squamous cell carcinoma, the overall survival was 74.1% in the UFT group and 60.7% in the control group (p=0.062) (**Table 2**, **Supplementary Fig. 1B**). The patients who were treated by radiotherapy tended to have a favorable prognosis (p=0.068) (**Table 2**, **Supplementary Fig. 1C**). However, the difference in the disease-free survival rates was not statistically significant (**Table 2**, **Fig. 1B**).

Next, we investigated the effect of long-term oral administration of UFT in the patients with cervical cancer. Among the UFT-treated patients, those who received the drug for ≥90 days had significantly higher overall and disease-free survival rates than those who received the drug for <90 days (p=0.001) (**Table 3**, **Fig. 2**). Long-term oral administration of UFT in patients with cervical cancer was associated with a decreased risk of recurrence and death. There was a significant difference in survival with the stage IV patients (57.1% in the patients who received the drug for ≥90 days vs. 17.1% in the patients who received the drug for <90 days) (**Table 3**). The difference in survival was significant in the patients with squamous cell carcinoma (81.0% in the patients who received the drug for ≥90 days vs. 59.6% in the patients who received the drug for <90 days) (**Table 3**). In the patients treated by radiotherapy, the overall survival rate was 74.9% for the long-term administration group and 44.7% for the shorter-term administration group (**Table 3**). Squamous cell carcinoma and radiotherapy had a significant effect on disease-free rates (p<0.05) (**Table 3**).

2. Toxicity

In total, 139 of the 162 patients enrolled in the UFT group were assessable for toxicity. Fifty-six patients (40.3%) showed ≥1 adverse reactions; overall, high-grade toxicities were infrequently observed. The toxicities are summarized according to the worst grade per patient for all treatment courses in **Table 4**. Nausea and vomiting (17/139, 12.2%), appetite loss (14/139, 10.1%), leukopenia/neutropenia (8/139, 5.8%), elevation of serum transaminases (7/139, 5.0%), diarrhea (7/139,

Table 4. Adverse events in the tegafur-uracil (UFT) group

Toxicity	Grade				
	1	2	3	4	Unknown
Hematological adverse events					
Leukopenia/neutropenia	1	6	1	0	0
Thrombocytopenia	0	1	0	0	0
Anemia	0	1	0	0	0
Elevation of serum transaminases	2	2	0	0	3
Non-hematological adverse events					
Nausea/vomiting	12	2	2	0	1
Loss of appetite	7	3	4	0	0
Diarrhea	3	3	1	0	0
Abdominal discomfort	2	0	0	0	0
Abdominal pain	1	1	1	0	0
Rash	4	0	0	0	0
Skin/nail pigmentation	3	2	0	0	0
Stomatitis	2	0	0	0	1
Itching	1	0	0	0	0
Tremor	1	1	0	0	0
Dysgeusia	3	0	0	0	0
General fatigue	0	0	0	0	1
Bloody stool	0	0	0	0	1
Total	42	22	9	0	7

5.0%), and skin/nail pigmentation (5/139, 3.6%) were the most commonly observed toxicities (**Table 4**). No patients developed grade 4 hematological or nonhematological adverse events. Overall, eight patients experienced grade 3 nonhematological adverse events in the study group. Gastrointestinal toxicity was not manageable for most patients. In particular, grade 3 hematological toxicity was observed in one patient.

DISCUSSION

This is the first report to investigate the efficacy of oral administration of a high dose (600 mg/day) of UFT in uterine cervical cancer patients. In this study, we elucidated that UFT maintenance treatment might lead to a favorable prognosis in stage III cases, in cases of squamous cell carcinoma, and in cases that were treated by radiotherapy.

One particular limitation of this study warrants mention. Owing to its small sample size, this study did not have sufficient statistical power to demonstrate the effect of UFT treatment in uterine cervical cancer patients. However, the overall survival rate was significantly higher in the UFT group than in the control group. This difference might indicate the possibility of using UFT as a treatment option in uterine cervical cancer patients.

DPD is the initial rate-limiting enzyme in the catabolism of 5-FU and plays a critical role in regulating the availability of 5-FU for anabolism. In the treatment of advanced colorectal cancer, orally administered prodrugs of 5-FU were introduced as DPD inhibitory fluoropyrimidine drugs, including UFT. UFT can maintain a higher 5-FU plasma level for a longer period through the inhibition of 5-FU degradation [2-4,13].

Adjuvant chemotherapy can offer clinical benefits for patients receiving primary radiation therapy because 5-FU is a radiation sensitizer. Theoretically, possible mechanisms such as the inhibition of repair of radiation damage, cell synchronization, recruitment of nonproliferating cells into the cell cycle, and reduction of the hypoxic fraction are promoted. In this study, we showed that the prognosis was favorable in the UFT group that was treated by radiotherapy. Compared with continuous infusion of 5-FU and capecitabine, the combination of UFT and radiotherapy has several clinical benefits. Chemoradiotherapy that includes UFT is efficacious against solid tumors, including those in head and neck cancer [14] and non-small cell lung cancer [15]. Recently, in the treatment of resectable rectal cancer, preoperative chemoradiotherapy consisting of UFT with leucovorin plus radiotherapy was well tolerated and effective, and it represents a convenient alternative to 5-FU-based chemoradiotherapy [16]. This study showed a correlation between the potential role of UFT and radiotherapy in uterine cervical cancer. There are some studies to evaluate the effect of adjuvant chemotherapy after chemoradiotherapy for locally advanced cervical cancer [17,18]. However, the evidence was insufficient to support the use of adjuvant chemotherapy after chemoradiotherapy in locally advanced cervical cancer. Future large trials are required to demonstrate a correlation between adjuvant chemotherapy including UFT and radiotherapy in uterine cervical cancer.

The effect of UFT has been suggested to be influenced by tumor angiogenesis and the status of angiogenesis-related factors as well as by the status of enzymes involved in 5-FU metabolism, such as TS and DPD [19-23]. In uterine cervical cancer, UFT and its metabolite gamma-butyrolactone inhibit angiogenesis induced by vascular endothelial growth factor, which causes an antitumor effect [24]. Metronomic therapy, which is continuously administered systemically at close to non-toxic doses, involves multiple mechanisms that include antiangiogenesis and antivasculogenesis. In this study, patients who received UFT administration for >90 days had significantly higher survival and disease-free rates than those who received the drug for <90 days. Long-term administration of UFT after primary treatment can be a key factor for improving the prognosis in uterine cervical cancer.

Our study suggested that high-dose oral UFT maintenance treatment might prolong the disease-free survival and overall survival of patients with uterine cervical cancer. However, adverse events are likely to be more frequently observed in patients treated with high-dose UFT (600 mg/day) than in those treated with low-dose UFT (300 to 400 mg/day). Although significant myelosuppression, mucositis, or alopecia was infrequently encountered, the incidence of gastrointestinal toxicity was shown to be approximately 32% in the present study, and most of these patients were not able to continue self-administration by mouth beyond 90 days. Recently, a weekday-on/weekend-off oral UFT schedule has been frequently proposed as outpatient adjuvant chemotherapy with good tolerability.

Future studies that investigate new treatment schedules should be considered to reduce the frequency of nausea/vomiting and loss of appetite while achieving an excellent rate of compliance in self-administering high-dose UFT therapy. High-dose UFT oral administration provides a springboard from which we expect to launch better adjuvant and maintenance chemotherapy in advanced cervical cancer. Our present regimen is a potentially attractive alternative to palliative treatments for recurrent and incurable cervical cancer.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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