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Original Article

Feasibility Trial of Oral UFT after Platinum-based Adjuvant Chemotherapy in Patients with Resected Non-small Cell Lung Cancer

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We evaluated the feasibility of maintenance treatment using UFT (a combination of tegafur and uracil) after adjuvant platinum-based chemotherapy in patients with resected lung cancer. A prospective feasibility trial was conducted. Between 2010 and 2014, UFT was administered for 2 years sequentially after platinum-based adjuvant chemotherapy in 24 patients with resected Stage IIA-IIIA non-small cell lung cancer. The safety of UFT and the rate of treatment completion were then evaluated. The prior platinum-based chemotherapy regimens consisted of cisplatin + vinorelbine in 16 patients, carboplatin + paclitaxel in 5 and carboplatin + S-1 in one. During the subsequent UFT administration, a total of 3 patients required a dose reduction because of Grade 1 blood-stained sputum, Grade 2 numbness, and Grade 2 constipation, in one patient each. Eleven patients underwent the planned 2-year UFT administration, but 12 patients could not because of the recurrence of lung cancer in 5 patients, metachronous malignancy in one, and toxicities in 6. The completion rate for UFT administration was 64.7% (11/17). The most common type of toxicity was gastrointestinal toxicities. All of the toxicities were grade 1 or 2, and no severe toxicities were observed. UFT treatment after platinum-based chemotherapy was revealed to be feasible.

Key words: UFT, adjuvant, chemotherapy, lung cancer, resection

Lung cancer is one of the most common forms of neoplasms and is the leading cause of cancer-related deaths in the world. The treatment of choice in patients with Stage I, Stage II and some subsets of Stage IIIA non-small cell lung cancer (NSCLC) is surgery. However, the 5-year survival rate after a complete resection for all stages is approx. 60%, and many patients develop recurrences [1]. To improve the outcomes after resection, adjuvant chemotherapy is recommended. Platinum-based chemotherapy has become a standard regimen in patients with resected Stage II or IIIa disease, and improvements in survival rates of 2-15% have been reported [2-5].

In patients with advanced lung cancer or recurrence, many trials have evaluated new agents and/or treatment strategies to improve patient survival. Some of these trials have examined maintenance therapy. Maintenance therapy is defined as a treatment that is performed after the initial cycles of chemotherapy to maintain the response to the initial treatment for a longer period of time. Patel *et al.* reported that maintenance chemotherapy using bevacizumab after platinum-based chemotherapy demonstrated an improvement in overall survival in patients with advanced lung cancer [6]. Other investigators have also reported that maintenance treatment using pemetrexed or gemcitabine improved the survival period [7,8]. Since then, maintenance

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treatment has become a treatment option for patients with advanced lung cancer or recurrence. Based on the success of maintenance treatment in patients with advanced lung cancer, maintenance treatment has also been applied as an adjuvant treatment in patients with complete resected NSCLC. Niho *et al.* reported the results of a feasibility trial using S-1 as a maintenance agent after the adjuvant administration of three cycles of cisplatin and docetaxel. They reported that the 6-month completion rate for maintenance treatment using S-1 after three cycles of cisplatin and docetaxel was 51.2%, and they did not meet their criterion for feasibility, although the toxicity of S-1 was acceptable. They concluded that modification of the S-1 treatment schedule might be necessary to improve compliance [9].

UFT is an oral anticancer agent that is a combination of tegafur and uracil in a molar ratio of 1 : 4. Although UFT is in the same category of anticancer agents as S-1, it is thought to have a milder adverse effect profile. We therefore considered that UFT might be a more suitable agent for maintenance treatment after platinum-based chemotherapy, and we conducted the following feasibility trial of maintenance treatment using UFT after adjuvant platinum-based chemotherapy in patients with resected lung cancer.

Patients and Methods

A prospective feasibility trial was conducted. This study was approved by our Institutional Review Boards No. 2016-130 and was conducted in compliance with the guidelines of good clinical practice and the principles of the Declaration of Helsinki. All of the patients provided written informed consent prior to study entry. The study was registered in the UMIN Clinical Trials Registry as UMIN000003204. Enrollment began in 2010 and closed in August 2014 (Fig. 1).

The criteria for patient eligibility were as follows: patients who underwent at least one cycle of platinum-based chemotherapy for completely resected Stage II-IIIA NSCLC, age > 20 years, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Other criteria included a PaO_2 at room air ≥ 70 torr or an SpO_2 at room air ≥ 95% and adequate organ function (*i.e.*, total bilirubin ≤ 1.5 mg/dL, AST and ALT ≤ 100 IU/L, leukocyte count ≥ 2,000 and ≤ 12,000/mm^3, neutrophil count ≥ 1,000/mm^3, hemoglobin ≥ 10.0 g dl/L, and platelets ≥ 75,000/mm^3). Patients were required to start the protocol UFT administration within 8 weeks after the prior platinum-based adjuvant chemotherapy. The key exclusion criteria were active infection; interstitial pneumonia as determined using CT of the chest; severe diarrhea; active concomitant malignancy; pregnancy or breast-feeding; and a history of hypersensitivity to UFT. Disease staging was performed according to the Union International Cancer Control (UICC) 7th TNM edition [10].

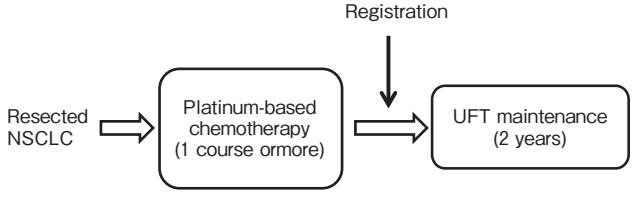

Fig. 1 Study protocol.

Administration of UFT. Daily oral UFT was initiated within 8 weeks after the prior adjuvant platinum-based chemotherapy, and this treatment was planned to continue for 2 years. The dose of UFT was selected according to each patient's body surface area (BSA) as follows: those with a BSA of ≤ 1.39 m^2 received 300 mg/day; those with a BSA of ≥ 1.40 m^2 but ≤ 1.79 m^2 received 400 mg/day; and those with a BSA of ≥ 1.80 m^2 received 500 mg/day. In the event of Grade 3 hematologic toxicity or Grade 2 non-hematologic toxicity, the administration of UFT was stopped until these factors recovered to the inclusion criteria levels and then was restarted at a one-rank lower dose. In the cases with an initial dose of 300 mg/day, treatment at a dose of 300 mg was resumed and the protocol was terminated if the toxicity reappeared.

Safety assessment and follow-up. A follow-up evaluation was performed every 3 months for the first 2 years and every 6 months thereafter. The evaluation included a physical examination, a complete blood count, blood chemical tests, screening for serum tumor markers, and chest radiography. A CT scan of the thorax and the upper abdomen were obtained every 6 months for the first 2 years after the operation and annually for the subsequent 3 years. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistical analysis. The primary endpoint was feasibility, which was defined as the proportion of patients who completed the 2-year UFT administration period; secondary endpoints were recurrence-free sur-

vival, overall survival, and safety. The sample size was calculated based on the following assumptions: a 2-year UFT treatment completion rate of 50%, with a rate of 30% being the lower limit of interest, and $\alpha = 0.05$ and $1-\beta = 0.8$; the estimated accrual number was 47 patients. The study was started in January 2010 but was terminated with 23 patients in August 2014 because of slow accrual.

Results

Patient background. Twenty-three patients were enrolled in UFT maintenance treatment after platinum-based chemotherapy. The characteristics of these 23 patients (17 males, 6 females) are listed in Table 1. The median age was 64 years (range 36-81 years). Histological examination revealed adenocarcinoma in 14 patients, squamous cell carcinoma in 6 patients, and others in 3 patients; the p-stage was p-Stage IIA in 12 patients, IIB in 2 and IIIA in 9. A segmentectomy was performed in 1 patient, a lobectomy was performed in 20 patients, and more extended resection was performed in 2 patients.

The prior platinum-based chemotherapy regimen was CDDP + VNR in 16 patients, CBDCA + PTX in 5 and CBDCA + S-1 in 1. Fourteen patients completed four cycles of chemotherapy, but the remaining nine patients did not.

UFT administration. After the platinum-based chemotherapies, the administration of UFT was initiated. Three patients required a dose reduction: Grade 1 blood-stained sputum, Grade 2 numbness, and Grade 2 constipation, in 1 patient each. Eleven patients completed the planned 2-year UFT administration, but the other 12 patients did not (Table 2). The reasons for the termination of UFT administration were the recurrence of lung cancer in 5 patients, a metachronous malignancy in 1, and toxicities in 6. The 6 patients who developed recurrences and metachronous malignancy were excluded from the calculation of the UFT completion rate, which was calculated to be 64.7% (11/17).

The toxicity profile for UFT is shown in Table 3. The most common type of toxicities was gastrointestinal toxicities. All of the toxicities were grade 1 or 2, and no severe toxicities were observed (Table 3).

Of the 14 patients who underwent 4 cycles of prior platinum-based chemotherapy, 8 patients completed the 2-year UFT administration, three patients discontinued UFT administration because of recurrence or metachronous malignancy, and 3 patients discontinued UFT treatment because of adverse effects. Of the 9 patients who did not undergo 4 cycles of prior chemotherapy, 3 patients completed the 2-year UFT administration, 3 patients discontinued UFT administration because of recurrence or metachronous malignancy,

Table 1 Patient characteristics

Age, years, median (range)		64 (36-81)
Male/Female		17/6
Stage		
	IIA/IIB/IIIA	12/2/9
Histological subtype		
	Adeno/Sq/Others	14/6/3
Extent of resection		
	Segmentectomy	1
	Lobectomy	20
	More extended resection	2
Prior chemo regimen		
	CDDP + VNR	16
	CBDCA + PTX	5
	CBDCA + S-1	2
Cycles of prior chemotherapy		
	4	14
	3	1
	2	3
	1	5

Adeno, adenocarcinoma; CBDCA, carboplatin; CDDP, cisplatin; PTX, paclitaxel; Sq, squamous cell carcinoma; VNR, vinorelbine.

Table 2 Administration of UFT

Duration of UFT administration (median, range)	14 (1-25)
2-year completion	11
1-2 years	2
0.5-1 year	3
< 0.5 years	7

Table 3 Toxicity of UFT

	G1	G2	≥G3
Nausea	1	1	0
Vomiting	1	0	0
Dysgeusia	1	0	0
Blood-stained sputum	1	0	0
Pneumonia	1	0	0
Constipation	1	0	0
Numbness	1	0	0

Table 4 Compliance with UFT treatment according to the number of cycles of prior chemotherapy

4 cycles of prior chemotherapy	14
Completion of 2-year administration	8
Discontinuation because of adverse effect	4
Discontinuation because of recurrence or second malignancy	3
1–3 cycles of prior chemotherapy	9
Completion of 2-year administration	3
Discontinuation because of adverse effect	3
Discontinuation because of recurrence or second malignancy	3

and 3 patients discontinued UFT treatment because of adverse effects (Table 4).

The median follow-up period was 48.5 months after registration. The 5-year recurrence-free survival rate was 69.3%, and the 5-year overall survival rate was 66.7%.

Discussion

Several studies have evaluated the efficacy of adjuvant treatment with UFT against lung cancer and other types of solid tumors [11, 12]. Wada *et al.* conducted a phase III trial and evaluated the efficacy of adjuvant UFT in patients with resected Stage I, II, or III lung cancer [13]. In their study, the patients were randomized into 3 groups: CDDP + VDS followed by 1-year UFT, 1-year UFT, and observation alone. The survival period was evaluated. The 5-year survival rates were 60.6% in the CDDP + VDS followed by 1-year UFT group, 64.1% in the 1-year UFT group, and 49.0% in the observation-alone group. These results demonstrated the efficacy of UFT in the setting of adjuvant treatment. Wada *et al.* included a regimen of CDDP + VDS followed by 1-year UFT in their study, although their administration period of UFT was 1 year and was different from our study. It is interesting and surprising that they conducted and included the CDDP + VDS regimen during a period when the concept of maintenance treatment was not common, although they did not refer to it as a maintenance treatment.

Kato *et al.* also reported a survival benefit of UFT administered as an adjuvant chemotherapy in patients with resected Stage I lung cancer [14]. Since then, adjuvant treatment using UFT has become a standard treatment option in Japan for patients with resected Stage I disease, especially those with T2a Stage IB disease. Platinum-based chemotherapy is recommended for patients with resected Stage II or IIIA diseases. In the present study, UFT was used as a maintenance agent after platinum-based chemotherapy in patients with resected Stage II or IIIA disease under the expectation that it would exert an additional effect.

A unique point of the present study was that it included patients who could not complete 4 cycles of platinum-based chemotherapy. The completion rate for 4 cycles of platinum-based adjuvant chemotherapy was reported to be 50-80%, and approximately one-third of the patients could not complete all 4 cycles of chemotherapy because of toxicities [4, 5, 15]. Ramsden *et al.* reported that a smaller dose of platinum-based chemotherapy was associated with a poorer survival outcome [16]. This indicated that patients who could not complete 4 cycles of chemotherapy might receive a smaller benefit than those who could. One of the purposes of the present study was to salvage those patients who could not undergo 4 cycles of chemotherapy and to improve their outcomes using UFT after incomplete platinum-based chemotherapy.

In this study, the nine patients who could not complete 4 cycles of chemotherapy underwent UFT administration. Of them, three patients discontinued UFT treatment because of toxicities, but the remaining 6 patients were able to undergo the administration of UFT for the planned 2 years or until recurrence. UFT administration was considered to be well tolerated in the patients who could not undergo 4 cycles of platinum-based chemotherapy. UFT was also administered to the 14 patients who completed 4 cycles of platinum-based chemotherapy. The completion rate for the 2-year UFT administration was 73%. Thus, UFT after platinum-based chemotherapy is considered to be feasible in both patients who are able to complete 4 cycles of platinum-based chemotherapy and those who cannot.

Niho *et al.* reported a similar feasibility trial using S-1 as a maintenance agent. They included 129 patients and administered 3 cycles of DOC + CDDP and then administered S-1; 106 patients completed the 3 cycles of DOC + CDDP. Of them, 66 patients (66/106 = 66.2%) underwent the UFT regimen for ≥ 6 months. In our present study, 16 patients (16/23 = 70.0%) were able to undergo the UFT regimen for ≥ 6 months. It is difficult to compare the results reported by Niho *et al.* with our results because the treatment protocols were different, but the compliance to S-1 and UFT appears to be com-

patible.

In this study, the completion rate for the 2-year UFT treatment was calculated as 64.7% (11/17). We excluded 6 patients who developed recurrences from this calculation. From an intent-to-treat standpoint, however, the completion rate should have been calculated using all 23 patients. In cases of platinum-based chemotherapy, the duration of treatment is approx. 2 or 3 months. The development of recurrences during this short period is relatively rare, and the number of cases requiring the discontinuation of chemotherapy because of recurrence can be ignored. On the other hand, the planned duration of UFT administration was as long as 2 years in this study. Six patients developed recurrences during the UFT treatment period and discontinued UFT treatment. The frequency of UFT discontinuation because of recurrence cannot be ignored, but we failed to consider this aspect when writing the protocol for this study. However, since the purpose of this study was to evaluate the feasibility and safety of UFT, we decided that it was reasonable to remove the 6 patients from the analysis of the completion rate.

Grade 1 adverse effects were observed in 3 patients, and a Grade 2 adverse effect was observed in 1 patient; Grade 3 or 4 adverse effects were not observed. None of the adverse effects were serious, and the UFT administration can be considered to have been tolerable; nevertheless, seven patients discontinued the treatment. Kato *et al*. also reported that the completion rate of the 2-year administration of UFT was as low as 61%, although the adverse effects were not serious. Although platinum-based chemotherapy is relatively toxic, preventative treatments and management strategies have been improved. Moreover, the treatment duration is limited to 3 months, and patients manage to endure four cycles of chemotherapy. In contrast, the treatment period of UFT was as long as 2 years. Although the adverse effects were not serious and were considered tolerable, longer treatment periods can be overwhelming, leading to the discontinuation of UFT treatment.

Another factor associated with the low compliance with UFT treatment might be a doctor-related factor. The patients enrolled in this study had already undergone standard platinum-based chemotherapy, and the physicians in charge of the patients' care might have decided to discontinue the UFT treatment relatively easily.

One of issues of this study is statistical reliability. The study size was designed to be 47 patients, but the study was stopped after the enrollment of 23 patients because of the slow accrual, and there is thus a concern about the statistical power to evaluate the primary end point. The completion rate was 64.7%, which is above the value of the primary end point of 50%. Although there is the concern about statistical power, the primary end point seems to have been accomplished, and the administration of UFT after platinum-based chemotherapy was considered feasible. The survival benefit delivered by UFT maintenance treatment was not determined in this study, since the number of the patients was too small to evaluate it. The utility of UFT maintenance after platinum-based chemotherapy should be confirmed in a large phase III trial.

In conclusion, UFT administration after platinum-based chemotherapy in patients with resected lung cancer was evaluated. The completion rate of the 2-year UFT administration was 64.7%, and no severe adverse effects were encountered. Thus, UFT maintenance treatment is considered to be feasible in this patient population.

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