A small randomized phase III single-center trial on postoperative UFT administration in patients with completely resected non-small cell lung cancer

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Our objective was to clarify the efficacy of UFT administration after the complete resection of non-small cell lung cancer (NSCLC) at a single-center institution, avoiding the biases produced by interinstitutional differences. A total of 30 patients who underwent the complete resection of NSCLC at our hospital between 1987 and 2001 were randomly assigned to a control group or to a UFT group (400 mg/day for 2 years). Thirteen patients were assigned to the control group and 17 patients were assigned to the UFT group. The overall survival rate, disease-free survival rate, patient compliance and adverse effect of the UFT treatment were then analyzed. The overall survival and disease-free survival rates of the UFT group were superior to those of the control group. Four patients in the UFT group received medication for 24 months and 14 patients were treated for more than 3 months. No severe adverse effects were observed. Seven patients suffered a relapse in the control group. Two patients suffered a relapse in the UFT group, but the relapse occurred after the discontinuation of UFT administration. We conclude that the administration of UFT as an adjuvant therapy prolonged the overall survival and disease-free survival rates of patients after the resection of NSCLC in a small study performed at a single institution. Interinstitutional differences, particularly operating procedures, should be carefully considered when performing large multicenter clinical studies. ***Anti-Cancer Drugs*** **15:29–33 © 2004 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2004, **15:**29–33

Keywords: adjuvant therapy, non-small cell lung cancer, UFT, surgery

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Received 10 June 2003 **Revised form accepted** 10 September 2003

Introduction

Non-small cell lung cancer (NSCLC) has a very poor prognosis and the relative 5-year survival rate is only 15% [1]. Surgery is the most effective treatment, but the recurrence rate is high, even if a complete resection is achieved. The 5-year survival rate for the resection of NSCLC all stage is 51.6%, while that for p-stage IA lesions is 79.2% in Japan [2]. In view of this poor outcome, adjuvant treatments such as chemotherapy or radiotherapy are highly desired, although many adjuvant trials have failed to obtain favorable results, with the exception of one UFT trail [3].

UFT is an anticancer drug that consists of FT (futraful) and uracil [4]. UFT is often administered as an adjuvant chemotherapy for the treatment of lung cancer and gastrointestinal cancer mostly in Japan [5]. Wada *et al.* conducted a multicenter randomized control study on the administration of UFT after the complete resection of NSCLC and determined that UFT administration prolonged the survival of patients [6].

In clinical trials, large numbers of cases are required to elucidate differences among groups; for this reason, multicenter trials are often performed. However, the subjects of the multicenter trials often form a heterogeneous population and the data collected from these trials may be subject to bias, despite the careful definition of inclusion and exclusion criteria. Operating procedures, in particular, are apt to differ among surgeons and institutions; these differences may affect patient survival. On the other hand, the subjects of a single-center trial are apt to form a more homogenous population, although the number of subjects in the study is likely to be much smaller than that of a multicenter trial. Here, we report the results of a prospective, randomized, non-blinded controlled trial on the administration of UFT after the complete resection of NSCLC that was conducted at our hospital to elucidate the efficacy of postoperative UFT administration.

Patients and methods

All subjects were less than 80 years old and had undergone the complete resection of stage IA to IIIA primary NSCLC at our hospital between September 1997 and January 2001. A complete resection was defined as a lobectomy or pneumonectomy with systematic lymph node dissection and the absence of microscopic malignant cells in the surgical margin [7]. None of the subjects had liver or renal dysfunctions, a history of another primary

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cancer, or postoperative complications. During this period, 83 cases were determined to be eligible for this trial; however, informed consent was not obtained in 53 patients, so only 30 patients were enrolled in the study.

The enrolled patients were randomly assigned to either a control group or to a UFT group, stratified according to age (< 65 or ≥ 65), sex (male or female), pathological stage (I, II or IIIA) and histology (squamous or others). The control group was followed-up using a monthly physical examination and chest X-ray for 2 years, and an examination of serum tumor markers (CEA and others) every 3 months. An abdominal and chest computed tomography was performed every 6 months. Beginning 2 years after the operation, the patients were followed-up using a physical examination, chest X-ray and serum tumor markers every 3 months. If the symptoms of a relapse, like headache by brain metastasis, occurred, appropriate examinations were performed. The UFT group received the same follow-up schedule as the control group in addition to oral administration of UFT 400 mg every day for 2 years, starting within 1 month of operation.

The overall survival rate and disease-free survival rates of the two groups, and the adverse effects and treatment compliance in the UFT were analyzed. Toxicities were evaluated according to the Japan Clinical Oncology Group criteria

The statistical analyses were performed using the Stata software package. Chi-square tests and *t*-tests were used to examine differences in patient background. Disease-free survival was calculated using the period between the operation day and the day of observed relapse. Overall survival was calculated using the period between the day of death or last observation and the operation day. The overall survival and disease-free survival curves were determined using the Kaplan–Meier method, and the survival and disease-free survival rate were tested for significance using a log-rank test. The hazard ratios were estimated using the Cox proportional hazard model. The level of statistical significance was set at $p \leq 0.05$.

Results

Table 1 shows the characteristics of the two groups. Thirteen patients were assigned to the control group and 17 patients were assigned to the UFT group. The difference in the number of patients in each group was due to the stratification of the patients. No differences in age, gender, histology, performance status, pathological stage, tumor size or operative procedure were observed between the two groups.

Table 2 shows the duration of UFT administration and the occurrence of adverse effects in the 17 patients belonging to the UFT group. In our study, the target duration of UFT administration was 24 months. Four of the 17 UFT patients were treated for 24 months, nine patients were treated for over 12 months, 12 patients were treated for over 6 months and 14 patients were treated for over 3 months. Nine patients experienced adverse effects, but no severe adverse effects occurred, with the exception of a gastric ulcer in one case. Four

Table 1 Patient characteristics

Characteristic	UFT ($n=17$)	Control ($n=13$)	Total ($n=30$)	p value
Age (years)				
mean ± SD	59.6 ± 12.1	63.2 ± 10.2	66.2 ± 11.3	0.39
range	35–77	46–75	35–77	
Gender (female/male)	6/11	6/7	12/18	0.547
Performance status				
0	14	9	23	0.400
1	3	4	7	
2				
Histology				
squamous	6	2	8	0.292
non-squamous	11	11	22	
Pathological stage				
T1N0M0	7	6	13	0.858
T2N0M0	4	4	8	
T1N1M0	1	1	2	
T2N1M0	1	1	2	
T3N0M0	2	0	2	
T3N1M0	1	0	1	
T3N2M0	0	0	0	
T1N2M0	0	0	0	
T2N2M0	1	1	2	
Maximum tumor size				
mean	3.06	3.25	3.14	0.77
median	3.2	3.2	3.2	
Operation				
pneumonectomy	2	3	5	0.410
lobectomy	15	10	25	

UFT group: UFT 400 mg was orally administered every day for 2 years after operation. Control group: UFT was not administered after operation. p values were obtained according to χ^2-tests or *t*-tests.

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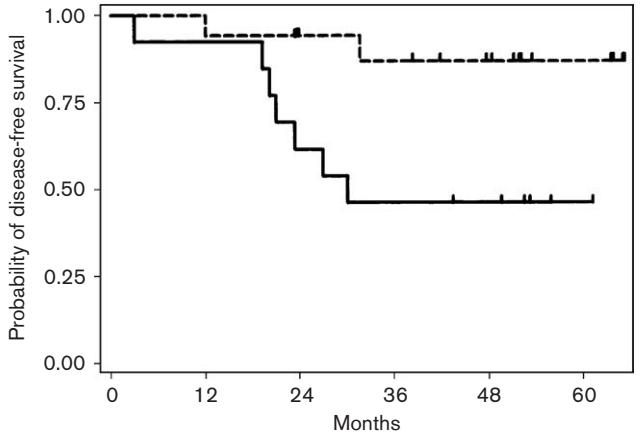
Table 2 Duration of UFT administration and the cause of cessation

Patient	Duration of UFT (months)	Cause of cessation	Grade of toxicity
1	1	gastric ulcer	3
2	1	nausea	2
3	1	visus muscarum	1
4	3	anorexia	1
5	3	no adverse effect; self cessation	0
6[a]	6	anorexia	1
7	6	no adverse effect; self cessation	0
8	10	acne	1
9	12	no adverse effect; self cessation	0
10	12	no adverse effect; self cessation	0
11	12	fatigue	1
12[b]	16	liver damage	2
13	20	herpes zoster	2
14	24	no adverse effect	0
15	24	no adverse effect	0
16	24	no adverse effect	0
17	24	no adverse effect	0

[a]Patient experienced a relapse 6 months after the cessation of UFT therapy and subsequently died.
[b]Patient experienced a relapse 1 year after the cessation of UFT therapy; presently alive.

Fig. 1

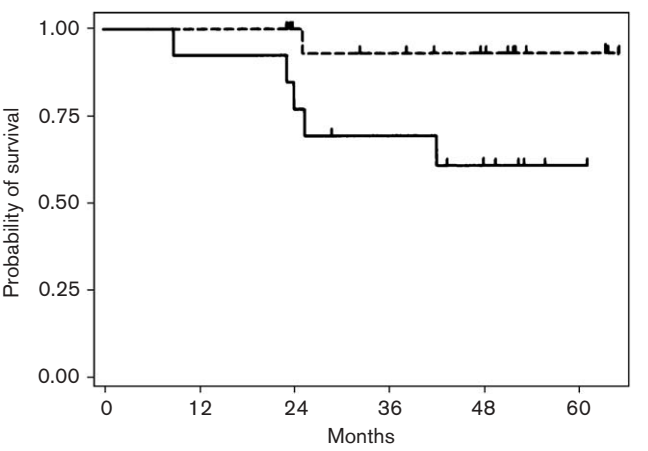


Disease-free survival curves for the UFT group (dotted line) and the control group (solid line).

patients decided to discontinue the UFT medication even though they had not experienced any adverse effects. The main reasons that the patients gave for deciding to discontinue the treatment were the cost of the drug and the fear of adverse effects.

Figure 1 shows the disease-free survival curves after surgery. The disease-free survival curve of the UFT group was superior to that of the control group throughout the entire period of the study. The 2- and 5-year disease-free survival rates of the control group were 62 and 46%, respectively. While those in the UFT group were 94 and 86%, respectively. A log-rank test showed a statistically significant difference in the disease-free survival rates of the two groups ($p = 0.016$). The hazard ratio for the UFT group compared to the control group was 0.18 (0.037–0.87); this value was statistically significant. When the three patients who took UFT for only 1 month were excluded from the analysis, a statistically significant difference ($p = 0.042$) in the disease-free survival rates was found using the log-rank test and the hazard ratio for the UFT group compared to the control group was 0.22 (0.047–1.08), according to the Cox proportional hazard model.

Fig. 2



Overall survival curves for the UFT group (dotted line) and the control group (solid line).

Figure 2 shows the overall survival curves. The overall survival curve of the UFT group was superior to that of the control group throughout the entire period of the study. The 2- and 5-year survival rates of the control group were 77 and 61%, respectively, while those of the UFT group were 100 and 93%, respectively. A log-rank test showed a statistically significant difference ($p = 0.046$) in the overall survival rates of the two groups and the hazard ratio was 0.15 (0.018–1.29), as assessed using the Cox proportional hazard model. When the three patients who took UFT for only 1 month were excluded from the analysis, the Kaplan–Meier curve of the UFT group was superior to that of the control group, but the difference was not statistically significant ($p = 0.0942$) according to the log-rank test; the hazard ratio was 0.15 (0.018–1.29) according to the Cox proportional hazard model.

In the control group, seven cases experienced a relapse. Of these seven patients, three patients had a stage IA tumor, one patient had a stage IB tumor, one patient had a stage IIA tumor, one patient had a stage IIB tumor and one patient had a stage IIIA tumor. Two of the cases with stage IA tumors are alive, and have had cancer for 4 months and 2 years, respectively. The other five cases

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died of cancer. In the UFT group, two cases with a stage IIB and IA tumor, respectively, experienced a relapse. The patient with the stage IA tumor in the UFT group is alive and has had cancer for 2 months, but the other case died of cancer. The recurrences in these patients were found 12 and 6 months after the discontinuation of UFT, respectively. No recurrences were observed during UFT administration in our series.

Discussion

In clinical trials, large numbers of cases are required to detect statistically significant differences among groups. To obtain large number of cases, multicenter studies rather than single-center studies are often used. However, operating procedures are apt to be different among institutions and these differences may influence the prognosis of patients attending the different institution. Bach *et al.* [8] described that patients who undergo resections for lung cancer at hospitals performing a large number of such procedures were likely to survive longer than patients who underwent such surgery at hospitals with a low volume of lung-resection procedures. In drug studies, the administration of the drug can be easily standardized, but the eligibility and exclusion criteria for the study must also be carefully specified. Wada *et al.* [6] clearly showed that UFT has an adjuvant effect, but 37 institutions were needed to accrue the 310 patients who participated in the study. The average number of patients from each institution was 310/37 = 8.4. Recently, Endo *et al.* [9] described that there was no significant prognostic advantage of UFT in the postoperative NSCLC. Their patients were randomly assigned to two groups with stratification of institution, histologic type and stage. However, the average number of patients from each institution was 221/21 = 10.0. Because the patient number per institution was small, interinstitutional bias should not be fully overcome even by stratification with institution and this study could not extract the prognostic advantage of UFT administration. We believed that a single-center study was needed to further clarify the adjuvant effect of UFT in a study that was not subject to interinstitutional bias.

The cytotoxic effect of UFT has been reported to be poor. A phase II study on the administration of UFT in patients with advanced and non-resectable NSCLC showed poor responses: 0/15(0%) and 2/7(28.3%), respectively [10,11]. However, we and Wada [6] have demonstrated that UFT has a potent adjuvant effect. Non-cytotoxic drugs sometimes have postoperative adjuvant effects. If another cytotoxic drug is present, the adjuvant effect should be further increased. However, drugs against NSCLC remain insufficient, even in a study where aggressive combination chemotherapy using a new third-generation chemotherapy regimen was used (50% response or lower) [12]. For adjuvant drug therapy after surgery, a cytotoxic effect is not absolutely necessary. Similar to the favorable clinical outcome produced by cytostatic drugs against some bacterial infections, cytostatic anticancer drugs would probably have a beneficial effect on postoperative chemotherapy. UFT has a low cytotoxic effect on NSCLC cells, but it inhibits micrometastasis [13,14], antilymphatic metastasis [15] and has an anti-angiogenic effect [16,17]. These effects should render an adjuvant effect.

The optimal duration of UFT administration is unclear, although the duration of UFT administration was 1 year in a previous study [6]. However, recurrences occurred in several NSCLC patients 2 years after their operation [2]. Since the action of UFT is cytostatic, rather than cytotoxic, we adopted 2 years in the present study. Four of our patients completed the treatment period and nine out of 17 patients received treatment for at least 1 year (including the patients treated for 2 years). The patients with relapses in the UFT group had not completed the treatment period and their relapses occurred 6 or 12 months after the discontinuation of UFT. No recurrences were observed during the period of UFT administration. Thus, a 2-year treatment period appears to be adequate.

As shown in Table 1, the number of subjects enrolled in our study was small. Thus, a stratification analysis of the data according to stage and histology cannot be performed, and further study is needed to clarify these points. However, the efficacy of UFT was clearly demonstrated in this single-center study. When multicenter trials are performed, data should be stratified according to the characteristics of the hospital in which the operative procedure was performed and it is better for a control study to have many patients per institution.

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