

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 22, 2004

VOL. 350 NO. 17

A Randomized Trial of Adjuvant Chemotherapy with Uracil–Tegafur for Adenocarcinoma of the Lung

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ABSTRACT

BACKGROUND

In a previous phase 3 trial of adjuvant chemotherapy after resection of non–small-cell lung cancer, a combination of uracil and tegafur (often referred to as UFT) taken orally was shown to prolong survival. A subgroup analysis disclosed that most patients who benefited had pathological stage I adenocarcinoma.

METHODS

We randomly assigned patients with completely resected pathological stage I adenocarcinoma of the lung to receive either oral uracil–tegafur (250 mg of tegafur per square meter of body-surface area per day) for two years or no treatment. Randomization was performed with stratification according to the pathological tumor category (T1 vs. T2), sex, and age. The primary end point was overall survival.

RESULTS

From January 1994 through March 1997, 999 patients were enrolled. Twenty patients were found to be ineligible and were excluded from the analysis after randomization; 491 patients were assigned to receive uracil–tegafur and 488 were assigned to observation. The median duration of follow-up for surviving patients was 73 months. The difference in overall survival between the two groups was statistically significant in favor of the uracil–tegafur group ($P=0.04$ by a stratified log-rank test). Grade 3 toxic effects occurred in 10 of the 482 patients (2 percent) who actually received uracil–tegafur.

CONCLUSIONS

Adjuvant chemotherapy with uracil–tegafur improves survival among patients with completely resected pathological stage I adenocarcinoma of the lung.

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N Engl J Med 2004;350:1713-21.

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THE COMBINATION OF URACIL AND tegafur (also referred to as UFT) at a molar ratio of 4:1 is an oral anticancer agent with good absorption in the small intestine.¹ Tegafur is a prodrug that is gradually converted to fluorouracil in the liver by the cytochrome P-450 enzyme. Uracil enhances the serum concentration of fluorouracil by competitive inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for fluorouracil catabolism.² Oral uracil–tegafur generates a higher maximal plasma level of fluorouracil than the protracted intravenous injection of fluorouracil given in a dose that is equimolar to the amount of tegafur in uracil–tegafur.³

In patients with advanced non–small-cell lung cancer, the rate of response to treatment with uracil–tegafur ranges from 6 percent to 8 percent,^{4,5} and a regimen of daily uracil–tegafur for 2 or 3 weeks plus a bolus injection of cisplatin yields a response rate of 29 to 38 percent and a median survival of 8 to 13 months.^{6–8} In two trials of uracil–tegafur plus cisplatin with concurrent radiotherapy in patients with locally advanced non–small-cell lung cancer, the response rates were 80 percent⁹ and 94 percent,¹⁰ with a median survival of 16.5 months.⁹ The results with uracil–tegafur plus cisplatin are similar to the results of other regimens of cisplatin-based combination chemotherapy.^{11,12}

The West Japan Study Group for Lung Cancer Surgery reported that survival was significantly longer in patients assigned to adjuvant treatment with uracil–tegafur than in patients assigned to observation alone after complete resection of stage I, II, or III non–small-cell lung cancer.¹³ The five-year survival rate was 64 percent in the uracil–tegafur group and 49 percent in the control group ($P=0.02$). In a subgroup analysis, there was no significant difference in overall survival between the uracil–tegafur group and the control group among patients with squamous-cell carcinoma ($P=0.24$). In contrast, patients with adenocarcinoma in the uracil–tegafur group had a significantly better survival than those in the control group ($P=0.009$).¹⁴ In addition, most patients with adenocarcinoma had stage I disease. These results prompted us to conduct a randomized trial of uracil–tegafur as a postoperative adjuvant treatment for patients with completely resected stage I adenocarcinoma.

METHODS

PATIENTS

Enrollment began in January 1994. Eligible patients had undergone a complete surgical resection of a pathologically documented stage I (T1N0M0 or T2N0M0) adenocarcinoma of the lung (according to the 1986 classification of the American Joint Committee on Cancer).¹⁵ Visceral pleural involvement was classified according to the rules of the Japan Lung Cancer Society,¹⁶ and a tumor that was larger than 3 cm in diameter or a tumor of any size that was exposed on the visceral pleural surface was classified as a pathological T2 tumor. Other inclusion criteria were an age of 45 to 75 years; the absence of preoperative anticancer treatment, previous cancer, and synchronous multiple cancers; an Eastern Cooperative Oncology Group (ECOG) performance status¹⁷ of 0, 1, or 2; a leukocyte count of at least 4000 per cubic millimeter; a platelet count of at least 100,000 per cubic millimeter; a hemoglobin level of at least 100 g per liter; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; and an absence of severe postoperative complications, such as pneumonia or empyema. Written or oral informed consent was obtained from all patients or their representatives, and the study was approved by the institutional review board of each participating center.

Confirmation of eligibility and randomization were performed by telephone or fax at a central site within 28 days after each patient's operation. All eligible patients were stratified according to age (less than 65 years vs. 65 years or older), sex, and pathological tumor category (T1 vs. T2).¹⁸

TREATMENT

Patients assigned to the control group were observed, with no treatment after surgery. In the treatment group, uracil–tegafur (250 mg of tegafur per square meter of body-surface area per day) in the form of 100-mg capsules (100 mg of tegafur plus 224 mg of uracil) was given orally before meals twice daily for two years, starting four weeks postoperatively. The dose was rounded up or down to the nearest 100 mg. Most patients received two capsules of uracil–tegafur (200 mg of tegafur and 448 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the capsules as prescribed.

Toxic effects of uracil-tegafur were graded according to the criteria of the Japan Society of Clinical Oncology, which consist of the World Health Organization criteria with minor modifications.¹⁹ If a grade 2 adverse reaction occurred, the dose of uracil-tegafur was reduced to 200 mg per square meter. Treatment was stopped if there was a grade 3 or higher adverse reaction, a leukocyte count of less than 3000 per cubic millimeter, a platelet count of less than 70,000 per cubic millimeter, a hemoglobin level of less than 9.5 g per deciliter, or an aspartate aminotransferase or alanine aminotransferase level that was more than three times the upper limit of the normal range.

FOLLOW-UP

A follow-up evaluation was performed every three months for the first two years after the operation and every six months thereafter. The evaluation included a physical examination, a complete blood count, blood chemical tests, screening for serum tumor markers, and chest radiography. A computed tomographic (CT) scan of the thorax and brain and either a CT scan or a sonogram of the upper abdomen were obtained every six months for the first two years after the operation and at least twice during the subsequent three years. Whenever possible, a biopsy of any new lesion suspected of being a recurrence or a second primary cancer was performed. A final diagnosis of such lesions was made by the physician in charge.

STATISTICAL ANALYSIS

The primary end point was overall survival; secondary end points were cancer-free survival and safety. All eligible patients were included in the analysis of overall survival and cancer-free survival, and all patients who were given uracil-tegafur were included in the safety assessment.

The sample size was calculated by the method of Schoenfeld and Richter²⁰ according to the following assumptions: a five-year survival rate of 70 percent in the no-treatment group, a hazard ratio for death of 0.67 in the uracil-tegafur group, a two-year accrual period, a five-year follow-up, a one-sided significance level of 0.05, and a statistical power of 80 percent. Since these calculations resulted in a sample size of 518 patients, the sample size was determined to be 600, with an allowance of about 15 percent for ineligible patients or patients who were lost to follow-up. In May 1995, the sample size was expanded to 984 patients after it became clear that the

five-year survival rate for those in the control group was better than expected. The newly adopted five-year survival rate was 83 percent, and the accrual period was extended to three years. A committee for efficacy and safety provided independent monitoring of the study. Haybittle-Peto horizontal boundaries,²¹ with a criterion of $P < 0.001$, were used in the interim analyses conducted to determine whether the study should be terminated early.

Overall survival was defined as the time from surgery until death from any cause, and cancer-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, a second cancer, or death from any cause. Survival was estimated by the Kaplan-Meier method, and any differences in survival were evaluated with a stratified log-rank test. Multivariable analyses with the Cox proportional-hazards model were used to estimate the simultaneous effects of prognostic factors on survival.²² Interactions with prognostic factors were also examined with the Cox proportional-hazards model. The SAS statistical software package (version 6.09, SAS Institute) was used for all calculations. Differences were considered to be statistically significant when the P value was 0.05 or less. All statistical tests were two-sided.

The protocol committee of the Japan Lung Cancer Research Group designed the study. Taiho Pharmaceutical Company collected and analyzed the data, and the authors interpreted the data and wrote the report. The authors had access to the primary data.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 1994 through March 1997, 999 patients were enrolled and randomly assigned to receive uracil-tegafur (498 patients) or no treatment (501 patients). Seven patients in the uracil-tegafur group and 13 patients in the control group were ineligible for the following reasons: pathological N1 or M1 disease in 7 patients, histologic findings other than adenocarcinoma in 6, no laboratory data at registration in 2, and miscellaneous reasons in 5. Therefore, there were 491 eligible patients in the uracil-tegafur group and 488 in the control group. Table 1 lists the base-line clinical characteristics of the two groups, which did not differ significantly. All but one patient in each group underwent lobectomy.

Table 1. Base-Line Characteristics of the Patients.

Characteristic	Uracil–Tegafur Group (N=491)	Control Group (N=488)
Age		
Mean (yr)	62	62
Range (yr)	45–75	45–75
<65 yr (no.)	274	275
≥65 yr (no.)	217	213
Female sex (no.)	253	249
ECOG performance status (no.)*		
0	376	369
1	105	113
2	10	6
Pathological tumor stage (no.)		
T1	362	354
T2	129	134
Invasion of pleura (no.)†		
0	340	346
1	120	114
2	29	28
Unknown	2	0
Tumor size (no.)		
≤2 cm	208	204
>2 to ≤3 cm	174	170
>3 cm	109	114
Location of the tumor (no.)		
Right upper lobe	182	189
Right middle lobe	41	34
Right lower lobe	102	87
Right lobes	2	2
Left upper lobe	107	114
Left lower lobe	54	60
Left lobes	3	2
Type of surgery (no.)		
Lobectomy	490	487
Pneumonectomy	1	1

* ECOG denotes Eastern Cooperative Oncology Group. Higher performance-status numbers indicate greater impairment.

† 0 indicates a tumor with no pleural involvement or a tumor that reaches the visceral pleura but does not extend beyond the elastic layer, 1 a tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface, and 2 a tumor that is exposed on the pleural surface but does not involve the parietal pleura.

ADVERSE REACTIONS AND COMPLIANCE

Of the 498 patients originally assigned to the uracil–tegafur group, 482 actually received uracil–tegafur. Few severe adverse reactions were associated with

uracil–tegafur. A grade 3 adverse reaction developed in 10 of 482 patients (2 percent), and no grade 4 adverse reactions occurred (Table 2).

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence or second cancer and those who died. The rate of compliance was 80 percent (95 percent confidence interval, 77 to 84 percent) at 6 months, 74 percent (95 percent confidence interval, 70 to 78 percent) at 12 months, 69 percent (95 percent confidence interval, 65 to 73 percent) at 18 months, and 61 percent (95 percent confidence interval, 57 to 66 percent) at 24 months. The main reasons for discontinuation of uracil–tegafur were an adverse reaction (in 123 patients), the patient's decision (52 patients), and the doctor's judgment (34 patients).

OVERALL SURVIVAL

The median follow-up among surviving patients was 72 months in the uracil–tegafur group and 73 months in the control group. Data were censored for 426 patients in the uracil–tegafur group and 399 in the control group. At the last follow-up visit, 65 patients in the uracil–tegafur group and 89 in the control group had died, and the overall survival rates in the two groups differed significantly on the basis of the stratified log-rank test (Fig. 1A). The five-year overall survival rate was 88 percent (95 percent confidence interval, 85 to 91 percent) in the uracil–tegafur group and 85 percent (95 percent confidence interval, 82 to 89 percent) in the control group. When the survival analysis was performed with the inclusion of all 999 randomized patients, the result did not change ($P=0.047$).

The predetermined covariates were age (<65 years vs. ≥65 years), sex, ECOG performance status (0 vs. 1 or 2), pathological T status (T1 vs. T2), and the assigned treatment. The covariates were selected according to multivariate analysis with the use of a stepwise procedure. All P values were less than 0.05. The selected covariates were as follows: age (hazard ratio for patients ≥65 years, 2.02; 95 percent confidence interval, 1.46 to 2.80; $P<0.001$), sex (hazard ratio for women, 0.66; 95 percent confidence interval, 0.48 to 0.91; $P=0.01$), T category (hazard ratio for T2, 1.95; 95 percent confidence interval, 1.41 to 2.69; $P<0.001$), and treatment group (hazard ratio for the uracil–tegafur group, 0.72; 95 percent confidence interval, 0.53 to 1.00; $P=0.05$).

Table 2. Adverse Reactions to Uracil-Tegafur.

Adverse Reaction	Grade of Toxicity*			
	1	2	3	4
	% of patients			
Leukopenia	2	1	0	0
Thrombocytopenia	<1	0	0	0
Anemia	1	<1	0	0
Increase in bilirubin	1	<1	0	0
Increase in aspartate aminotransferase	6	2	<1	0
Increase in alanine aminotransferase	6	2	0	0
Increase in alkaline phosphatase	2	<1	0	0
Anorexia	9	8	1	0
Nausea or vomiting	10	3	1	0
Diarrhea	2	1	<1	0
Alopecia	<1	0	0	0

* Toxicity was graded according to criteria of the Japan Society of Clinical Oncology. Grades range from 1 to 4, with a higher grade indicating a more severe reaction.

We also evaluated interactions between the four prognostic factors (sex, age, pathological tumor category, and size of the tumor) (Fig. 2) and the treatment. We included tumor size in the analysis because the tumor category is determined mainly by the maximal diameter of the primary tumor. As Figure 2 shows, there were significant interactions between the tumor category and size of the tumor and the treatment.

The survival rate among patients with T2 disease in the uracil-tegafur group was significantly higher than that in the control group, whereas among patients with T1 disease, there was no significant difference in survival between the uracil-tegafur and control groups. The five-year survival rate among patients with T2 disease was 85 percent (95 percent confidence interval, 79 to 91 percent) in the uracil-tegafur group and 74 percent (95 percent confidence interval, 66 to 81 percent) in the control group (Fig. 1B). The difference in overall survival between the two groups was statistically significant (P=0.005 by the log-rank test). The five-year survival rate among patients with T1 disease was 89 percent in the uracil-tegafur group and 90 percent in the control group (Fig. 1C). In the subgroups of patients with a tumor that was less than 2 cm in diameter, 2 to 3 cm, and greater than 3 cm, the five-year survival rate was 89 percent, 89 percent, and 85 per-

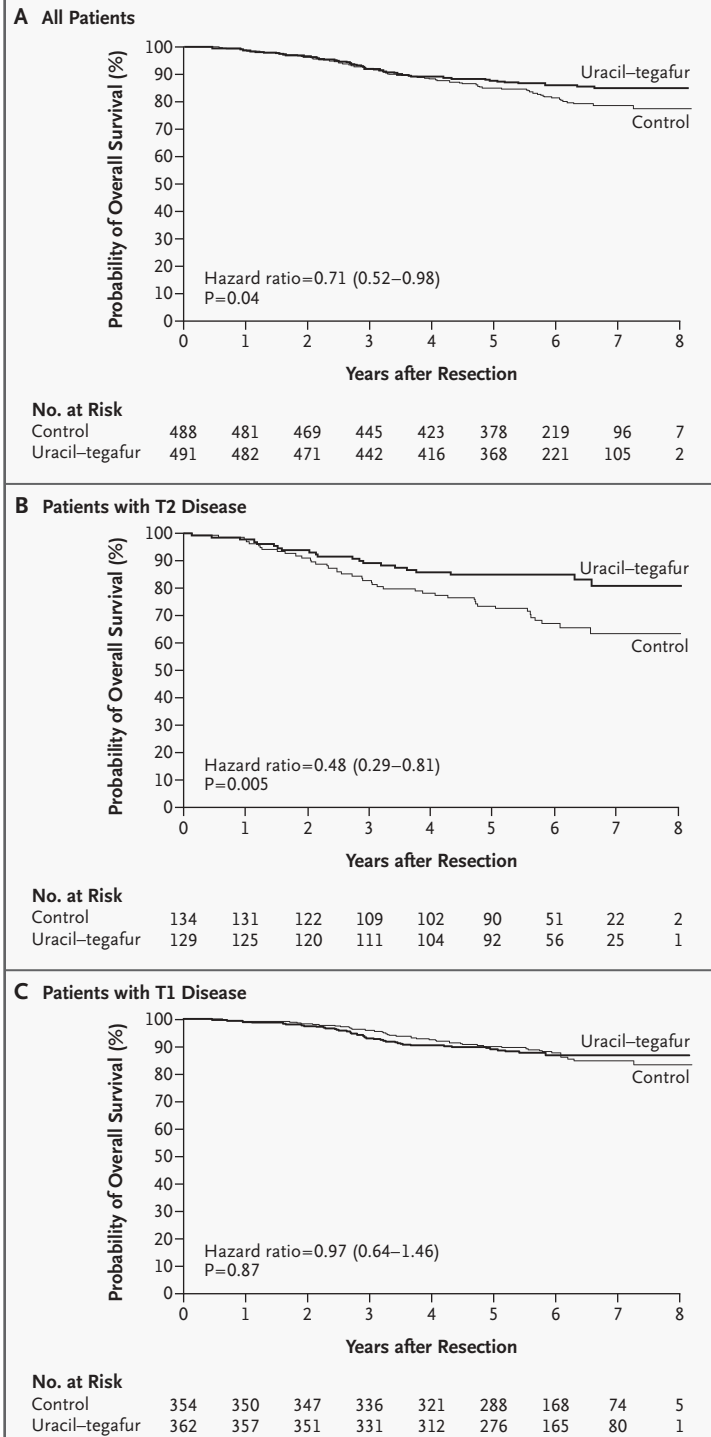


Figure 1. Overall Survival among All 979 Eligible Patients (Panel A), 263 Patients with T2 Disease (Panel B), and 716 Patients with T1 Disease (Panel C) Who Were Randomly Assigned to the Uracil-Tegafur Group and the Control Group.

The hazard ratios indicate the risk of death in the uracil-tegafur group as compared with the control group; 95 percent confidence intervals are shown in parentheses. P values were calculated with the use of the stratified log-rank test.

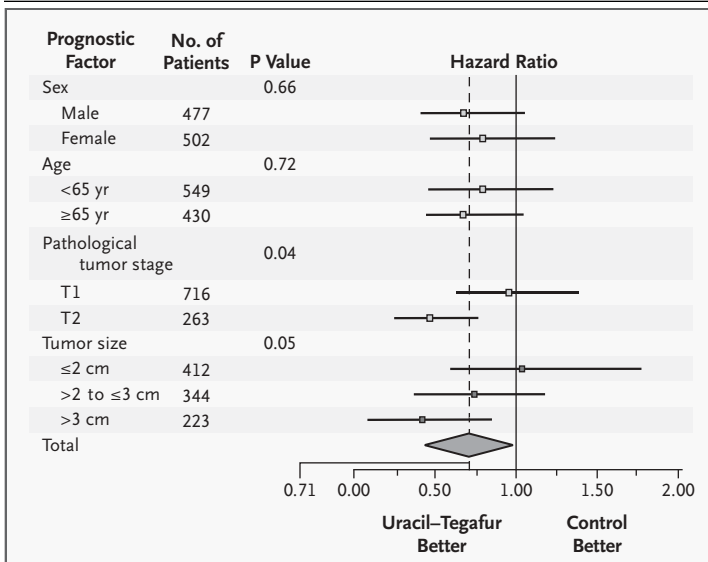


Figure 2. Hazard Ratios for Death in Patients in the Uracil–Tegafur Group as Compared with the Control Group, According to Four Prognostic Factors.

Each square represents the estimated treatment effect, the horizontal lines represent the 95 percent confidence intervals, and the diamond corresponds to the 95 percent confidence intervals for the entire group of patients. The P value for the tumor size is for the comparison of patients who had tumors that were 2 cm or less in diameter with patients who had tumors that were more than 3 cm.

cent, respectively, in the uracil–tegafur group and 91 percent, 86 percent, and 74 percent, respectively, in the control group.

PATTERN OF FAILURE AND CANCER-FREE SURVIVAL

A recurrence or a second primary cancer as the first treatment failure after surgery was documented in 23 percent of the uracil–tegafur group and 26 percent of the control group (Table 3). Among the 716 patients with T1 disease, recurrence or a second primary cancer was observed in 69 of 362 patients (19 percent) in the uracil–tegafur group and 76 of 354 patients (21 percent) in the control group; among the 263 patients with T2 disease, 42 of 129 patients (33 percent) in the uracil–tegafur group and 53 of 134 patients (40 percent) in the control group had recurrence or a second primary cancer as the first treatment failure. On the basis of a Kaplan–Meier analysis, the difference in cancer-free survival between the two groups was not statistically significant (P=0.25 by the stratified log-rank test). The survival of patients after the diagnosis of a recurrence or a second primary cancer did not differ significant-

ly between the groups (P=0.14 by the log-rank test): the one-year and two-year survival rates after diagnosis were 65 percent and 50 percent, respectively, in the uracil–tegafur group and 65 percent and 42 percent, respectively, in the control group.

DISCUSSION

The Japanese Association for Chest Surgery and Japan Lung Cancer Society recently reported the long-term survival rate of 7408 patients with lung cancer who had undergone a surgical resection in 1994, the year that our trial started.²³ The main histologic types were adenocarcinoma (in 56 percent of the patients) and squamous-cell carcinoma (in 33 percent). Among patients with pathological stages T1N0M0 and T2N0M0, the five-year survival rates were 79 percent and 60 percent, respectively. In our study of adenocarcinoma, the five-year survival rate in the control group was 90 percent among patients with T1N0M0 disease and 74 percent among those with T2N0M0 disease. Although the figures in the two studies cannot be directly compared, owing to different histologic patterns and times when the data were collected, the excellent five-year survival rate for the control patients in our study^{24,25} indicates that our collaborative group has made improvements in the quality of the surgical treatment and the accuracy of surgical staging.

Our study shows that adjuvant chemotherapy with uracil–tegafur has a beneficial effect on the survival of patients with resected stage I adenocarcinoma of the lung. This benefit, however, was not observed in patients with T1N0 disease. In the past few years, the number of patients in whom small adenocarcinomas have been discovered has increased owing to the increased use of computed tomography. In our study, 412 of 979 patients (42 percent) had an adenocarcinoma that was less than 2 cm in diameter. Adenocarcinomas of this size often include bronchoalveolar carcinoma, which is unlikely to recur after resection.²⁶ Therefore, a small adenocarcinoma usually has a very good prognosis^{26,27}; in our study, the five-year survival rate of patients with tumors that were 2 cm or less in diameter was 91 percent. For this reason, we believe that patients with small tumors should be excluded from adjuvant trials unless a subgroup with a poor prognosis is identified.

In contrast, treatment with uracil–tegafur tended to improve the survival rate among patients with a tumor that was 2 to 3 cm in diameter and provided

a definitive survival benefit for patients with a tumor that was more than 3 cm in diameter. These findings indicate that the effect of uracil-tegafur may be related to certain biologic factors. In a retrospective study, Tanaka et al.²⁸ found that the prognosis was good for patients with non-small-cell lung cancer characterized by a high apoptotic index and no aberrant expression of p53 who received postoperative uracil-tegafur.

Patient compliance is usually a problem in trials of adjuvant chemotherapy. In trials of cisplatin-based chemotherapy, which was scheduled to be administered in three or four cycles postoperatively, only 50 to 70 percent of the planned treatment was given.²⁹⁻³² In our trial, we planned to give uracil-tegafur daily for two years. However, only 61 percent of patients assigned to the treatment completed the two-year course. The main reasons for discontinuing uracil-tegafur were adverse reactions (which were infrequent and usually mild) and the patient's decision, which suggests that compliance in trials of adjuvant chemotherapy may not be related to the severity of adverse events.

The main difference between trials of cisplatin-based adjuvant chemotherapy and trials of adjuvant chemotherapy with uracil-tegafur is the duration of the treatment. The cisplatin-based regimens entail three or four cycles (9 to 16 weeks) of chemotherapy,²⁹⁻³² whereas uracil-tegafur is taken daily for 1 or 2 years.^{13,33-36} Fluorouracil is not a dose-dependent drug but a time-dependent agent. Therefore, a daily regimen of uracil-tegafur is an effective way of maintaining the blood level of fluorouracil. In addition, uracil-tegafur and its metabolites have an inhibitory effect on tumor angiogenesis in mice.³⁷ If this effect occurs in humans, then the daily, long-term administration of uracil-tegafur may be beneficial.

So far, six randomized trials,^{13,33-36} including

Table 3. Pattern of Treatment Failure.

Pattern	Uracil-Tegafur Group (N=491)	Control Group (N=488)
	no. of patients (%)	
Intrathoracic only		
Local recurrence	17	8
Pulmonary metastases	36	38
Local recurrence plus pulmonary metastases	3	12
Second cancer	11	11
Extrathoracic only		
Recurrence	23	33
Second cancer	14	18
Intrathoracic plus extrathoracic recurrence	7	9
Total	111 (22.6)	129 (26.4)

the present one, have been conducted that compare surgery alone with adjuvant chemotherapy with uracil-tegafur. Among them, three trials have shown a survival benefit from treatment with uracil-tegafur.^{13,34} A meta-analysis of those six trials showed that adjuvant chemotherapy with uracil-tegafur improved the overall survival (hazard ratio for death, 0.77; 95 percent confidence interval, 0.63 to 0.94; $P=0.01$).³⁸ It is unclear whether patients with stage II or stage III disease benefit from treatment with uracil-tegafur and whether treatment for one year is equivalent to treatment for two years. However, our study indicates that patients with completely resected stage I disease, especially T2N0 adenocarcinoma, will benefit from adjuvant chemotherapy with uracil-tegafur.

Supported by Taiho Pharmaceutical Company, Tokyo, Japan.

We are indebted to Professor J. Patrick Barron at the International Medical Communications Center, Tokyo Medical University, for his review of the manuscript.

APPENDIX

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REFERENCES

- Fujii S, Kitano S, Ikenaka K, Shirasaka T. Effect of coadministration of uracil or cytosine on the anti-tumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. *Gann* 1979;70:209-14.
- Ikenaka K, Shirasaka T, Kitano S, Fujii S. Effect of uracil on metabolism of 5-fluorouracil in vitro. *Gann* 1979;70:353-9.
- Ho DH, Pazdur R, Covington WP, et al. Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N₁-(2'-tetrahydrofuryl)-5-fluorouracil. *Clin Cancer Res* 1998;4:2085-8.
- Shimizu E, Kimura K, Sone S, et al. A phase II study of UFT in non-small cell lung cancer. *Gan To Kagaku Ryoho* 1986;13:2970-3. (In Japanese.)
- Keicho N, Saijo N, Shinkai T, et al. Phase II study of UFT in patients with advanced non-small cell lung cancer. *Jpn J Clin Oncol* 1986;16:143-6.
- Ichinose Y, Takanashi N, Yano T, et al. A phase II trial of oral tegafur and uracil plus cisplatin in patients with inoperable non-small cell lung cancer. *Cancer* 1995;75:2677-80.
- Ichinose Y, Yoshimori K, Yoneda S, Kuba M, Kudoh S, Niitani H. UFT plus cisplatin combination chemotherapy in the treatment of patients with advanced non-small cell lung carcinoma: a multiinstitutional phase II trial. *Cancer* 2000;88:318-23.
- Saito J, Nakai Y, Saijo Y, et al. A phase II trial of oral UFT plus cisplatin (CDDP) in patients with non-small cell lung cancer (NSCLC). *Lung Cancer* 2001;31:285-93.
- Ichinose Y, Nakai Y, Kudoh S, et al. UFT plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer (NSCLC): a multiinstitutional phase II trial. *Prog Proc Am Soc Clin Oncol* 2002;21:321a. abstract.
- Ichinose Y, Yano T, Asoh H, et al. UFT plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer. *Oncology (Huntingt)* 1999;13:Suppl 3:98-101.
- Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-8.
- Vokes EE, Herndon JE II, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B study 9431. *J Clin Oncol* 2002;20:4191-8.
- Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. *J Clin Oncol* 1996;14:1048-54.
- Okimoto N, Soejima R, Teramatsu T. A randomized controlled postoperative adjuvant chemotherapy trial of CDDP+VDS+UFT and UFT alone in comparison with operation only for non-small cell lung carcinomas (second study). *Jpn J Lung Cancer* 1996;36:863-71. (In Japanese.)
- Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89:Suppl:225s-233s.
- The Japan Lung Cancer Society. General rule for clinical and pathological record of lung cancer. 3rd ed. Tokyo, Japan: Kanehara, 1987.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
- Hamajima N, Japan Lung Cancer Research Group. Registration for a large-scale randomized controlled trial of postsurgical adjuvant chemotherapy for lung cancer in Japan. *Int J Clin Oncol* 1999;4:133-7.
- WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979:14-21. (Offset publication no. 48.)
- Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982;38:163-70.
- Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44:793-7.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Japanese Joint Committee of Lung Cancer Registry, Shirakusa T, Kobayashi K. Lung cancer in Japan: analysis of lung cancer registry for resected cases in 1994. *Jpn J Lung Cancer* 2002;42:555-66. (In Japanese.)
- Breathnach OS, Kwiatkowski DJ, Finkelstein DM, et al. Bronchioloalveolar carcinoma of the lung: recurrences and survival in patients with stage I disease. *J Thorac Cardiovasc Surg* 2001;121:42-7.
- Myrdal G, Lambe M, Gustafsson G, Nilsson K, Stahle E. Survival in primary lung cancer potentially cured by operation: influence of tumor stage and clinical characteristics. *Ann Thorac Surg* 2003;75:356-63.
- Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung: histologic characteristics and prognosis. *Cancer* 1995;75:2844-52.
- Kodama K, Higashiyama M, Yokouchi H, et al. Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. *Lung Cancer* 2001;33:17-25.
- Tanaka F, Otake Y, Yanagihara K, et al. Apoptosis and p53 status predict the efficacy of postoperative administration of UFT in non-small cell lung cancer. *Br J Cancer* 2001;84:263-9.
- Feld R, Rubinstein L, Thomas PA, Lung Cancer Study Group. Adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in patients with completely resected stage I non-small-cell lung cancer. *J Natl Cancer Inst* 1993;85:299-306.
- Ohta M, Tsuchiya R, Shimoyama M, et al. Adjuvant chemotherapy for completely resected stage III non-small-cell lung cancer: results of a randomized prospective study. *J Thorac Cardiovasc Surg* 1993;106:703-8.
- Ichinose Y, Tada H, Koike T, et al. A randomized phase III trial of postoperative adjuvant chemotherapy in patients with completely resected stage IIIa-N2 non-small cell lung cancer: Japan Clinical Oncology Group (JCOG 9304) trial. *Prog Proc Am Soc Clin Oncol* 2001;20:311a. abstract.
- Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003;95:1453-61.

33. Tanaka F, Wada H, West Japan Study Group for Lung Cancer Surgery. Postoperative oral administration of UFT for completely resected pathologic stage I non-small cell lung cancer: the West Japan Study Group for Lung Cancer Surgery (WJSG), the 4th study. *Prog Proc Eur Cancer Conf* 2001; 37:S29. abstract.
34. Tada H, Yasumitsu T, Iuchi K, Taki T, Kodama K, Mori T. Randomized study of adjuvant chemotherapy for completely resected non-small cell lung cancer: lack of prognostic significance in DNA ploidy pattern at adjuvant setting. *Prog Proc Am Soc Clin Oncol* 2002;21:313a. abstract.
35. Endo C, Saito Y, Iwanami H, et al. A randomized trial of postoperative UFT therapy in p stage I, II non-small cell lung cancer. *Lung Cancer* 2003;40:181-6.
36. Imaizumi M. A randomized trial of postoperative adjuvant chemotherapy for p-stage I non-small cell lung cancer (4th cooperative study). *Prog Proc World Conf Lung Cancer* 2003;41:S54. abstract.
37. Yonekura K, Basaki Y, Chikahisa L, et al. UFT and its metabolites inhibit the angiogenesis induced by murine renal cell carcinoma, as determined by a dorsal air sac assay in mice. *Clin Cancer Res* 1999;5:2185-91.
38. Hamada C, Ohta M, Wada H, et al. Efficacy of oral UFT for adjuvant chemotherapy after complete resection of non-small cell lung cancer: meta-analysis of six randomized trials in 2003 patients. *Prog Proc Eur Cancer Conf* 2003;39:S231. abstract.

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