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A randomized phase III trial of adjuvant treatment for resected non-small cell lung cancer in Japan

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Abstract Two randomized phase III trials [uracil–tegafur (UFT) and bestatin trials] of adjuvant treatment for resected stage I non-small cell lung cancer (NSCLC) have recently been completed in Japan. The Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy conducted a phase III trial in which 999 patients with completely resected stage I adenocarcinoma were assigned to receive either oral UFT [tegafur, 250 mg/(m^2 day)] for 2 years or no treatment (January 1994–March 1997). At a median follow-up time of 73 months, the overall survival in the UFT group was significantly higher than that in the control group ($P = 0.035$). Grade 3 toxic effects occurred in 10 of the 482 patients (2%) who received UFT. Since 1985 when UFT became available in Japan, a total of 6 phase III trials comparing adjuvant chemotherapy using UFT with observation alone, including the above trial, have been conducted. A meta-analysis of these six trials reconfirmed that UFT had a beneficial effect in patients with completely resected stage I NSCLC. A phase III trial comparing UFT with platinum-based chemotherapy in patients with completely resected NSCLC with pathological stage IB through IIIA disease is also now under consideration. Bestatin is a potent aminopeptidase inhibitor that has both immunostimulant and antitumor activities. A prospective randomized, double blind, placebo-controlled trial in patients with completely resected stage I squamous cell carcinoma was conducted. A total of 402 patients were randomly assigned to receive either oral bestatin 30 mg/day or a placebo daily for 2 years (July 1992–March 1995). At the median follow-up time of 76 months, the overall survival in the bestatin group was significantly higher than that of the placebo control group ($P = 0.033$). The 5 year overall survival was 81% in the bestatin group and 74% in the placebo group. Few adverse events were observed in either group. These results, however, require further confirmation in other phase III trials.

Keywords Non-small cell lung cancer · Postoperative adjuvant treatment · UFT · Bestatin · Stage I

Introduction

Two randomized phase III trials [uracil–tegafur (UFT) and bestatin trials] of adjuvant treatment for resected stage I non-small cell lung cancer (NSCLC) have recently been completed in Japan.

UFT trial

UFT is an oral anticancer agent composed of tegafur and uracil at a molar ratio of 1:4, which has good absorption from the small intestine [6]. Tegafur is gradually converted to 5-fluorouracil via the metabolism of liver enzyme P450. Uracil enhances the serum 5-fluorouracil concentration by the competitive inhibition of

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dihydropyrimidine dehydrogenase, the enzyme responsible for 5-fluorouracil catabolism [11]. Administration of oral UFT reportedly generates a higher maximum plasma level of 5-fluorouracil than the protracted intravenous injection of 5-fluorouracil given in a dose equimolar to the tegafur in UFT [9].

The West Japan Study Group for Lung Cancer Surgery reported that postoperative adjuvant treatment with UFT in patients with completely resected stage I–III disease prolonged survival significantly compared with observation alone [33]. The 5 year survival rate was 64% in the UFT group and 49% in the control group ($P = 0.02$). In a subgroup analysis, no statistically significant difference between the two groups was observed in the overall survival of patients with squamous cell carcinoma ($P = 0.24$). In contrast, patients with adenocarcinoma in the UFT group had a significantly better survival than those in the control group ($P = 0.009$) [21]. Of note, most patients with adenocarcinoma had stage I disease. Those results prompted us to conduct a prospective randomized trial of UFT as a postoperative adjuvant treatment for patients whose stage I adenocarcinoma was completely resected.

Between January 1994 and March 1997, 999 patients who had undergone a complete resection of a pathologically documented stage I (T1–2, N0, M0) [18] adenocarcinoma were enrolled in the trial. Patients were randomly assigned to receive either no treatment ($n = 501$) or UFT ($n = 498$), respectively. However, 13 patients in the control group and 7 patients in the UFT group were found to be ineligible. Therefore, the number of all eligible patients was 488 in the control group and 491 in the UFT group. The patients assigned to the control group were observed with no further treatment after surgery. In the UFT group, UFT (tegafur 250 mg/m^2 of body-surface area) in the form of a 100 mg capsule (100 mg tegafur and 224 mg uracil) was given orally in two separate doses, before meals, daily for 2 years, starting 4 weeks after surgery. The clinical characteristics of those eligible patients are listed in Table 1. There were no statistically significant differences in the baseline characteristics of the patients. All but one patient in each group underwent lobectomy.

Of the 498 patients randomized to the UFT group, 482 patients received oral UFT. Table 2 lists the incidence of UFT-related adverse reactions. Few severe adverse reactions were associated with UFT administration. There was no grade 4 adverse reaction. In total, 10 (2%) of 482 patients developed a grade three adverse reaction.

The median follow-up for the surviving patients was 72 months in the UFT group and 73 months in the control group. The 5 year survival rate was 88% [95% confidence interval (CI): 85–91%] in the UFT group and 85% (95% CI: 82–89%) in the control group (Fig. 1).

Table 1 Patient characteristics in the UFT study

Characteristic	UFT ($n = 491$)	Control ($n = 488$)
Age		
Mean (years)	62	62
Range (years)	45–75	45–75
<65	274	275
≥65	217	213
Female sex	253	249
ECOG performance status[a]		
0	376	369
1	105	113
2	10	6
Pathological T status		
T1	362	354
T2	129	134
Pleural invasion[b]		
0	340	346
1	120	114
2	29	28
Unknown	2	0
Tumor size		
≤2 cm	208	204
>2 to ≤3 cm	174	170
>3 cm	109	114
Location of the tumor		
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
Operation modality		
Lobectomy	490	487
Pneumonectomy	1	1

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[a] ECOG Eastern Cooperative Oncology Group. Higher performance status numbers indicate greater impairment

[b] *0* 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

The predetermined covariates were age (<65 vs ≥65 years), sex (male vs female), performance status (0 vs 1 + 2), T status (T1 vs T2), and treatment group. The covariates were selected according to multivariate analysis using a stepwise procedure under the condition that the *P*-value was less than 0.05. The selected covariates were as follow: age (hazard ratio = 2.02, 95% CI: 1.46–2.80; $P < 0.001$), T status (hazard

Table 2 Adverse reactions to UFT ($n = 482$)

Adverse reaction	Grade of toxicity[a]			
	1	2	3	4
Percent 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 AST	6	2	<1	0
Increase in ALT	6	2	0	0
Increase in ALP	2	<1	0	0
Anorexia	9	8	1	0
Nausea/vomiting	10	3	1	0
Diarrhea	2	1	<1	0
Alopecia	<1	0	0	0

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[a] 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

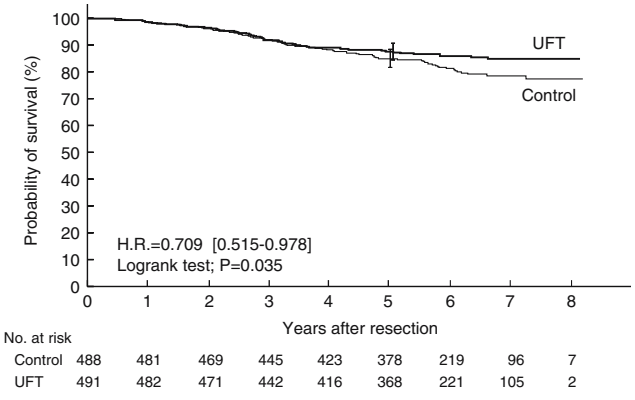

Fig. 1 Overall survival of all eligible patients ($n = 979$). *Error bars* represent the 95% confidence intervals. Reprinted with permission from the New England Journal of Medicine [15]. Copyright© 2004 Massachusetts Medical Society. All rights reserved

ratio = 1.95, 95% CI: 1.41–2.69; $P < 0.001$), sex (hazard ratio = 0.66, 95% CI: 0.48–0.91; $P = 0.01$), and treatment group (hazard ratio = 0.72, 95% CI: 0.53–1.00; $P = 0.05$).

The interaction between four prognostic factors and the treatment was then evaluated (Fig. 2). Since the T status is mainly classified by the maximum diameter of the primary tumor, we added the tumor size to the analysis. As shown in Fig. 2, a significant interaction between either T status or the tumor size with the treatment was observed.

The patients with T2 disease in the UFT group had a significantly better survival than those in the control group, while there was no survival difference between the UFT and the control group in the patients with T1 disease. The 5 year survival rate of patients with T2 disease

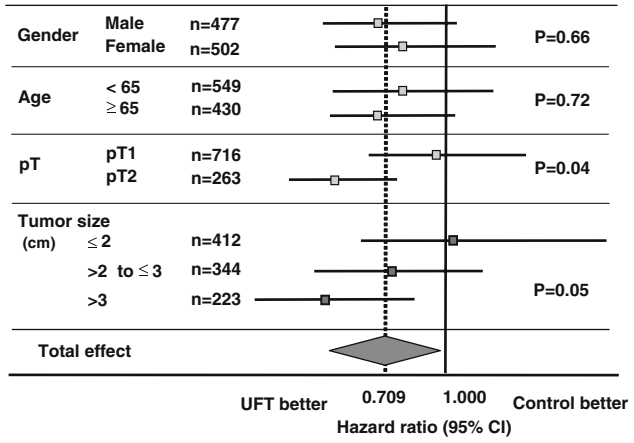

Fig. 2 Hazard ratios for death in patients in the UFT group compared with the control group, according to four prognostic factors. Each square represents the estimated treatment effect, and the horizontal lines represent the 95% confidence intervals. The diamond corresponds to the 95% confidence intervals 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 patents who had tumors that were more than 3 cm. Reprinted with permission from the New England Journal of Medicine [15]. Copyright© 2004 Massachusetts Medical Society. All rights reserved

was 85% (95% CI: 79–91%) in the UFT group and 74% (95% CI: 68–81%) in the control group (Fig. 3). The overall survival between the two groups was statistically significantly different ($P = 0.005$ by the log-rank test). The 5 year survival rate of patients with T1 disease was 89% in the UFT group and 90% in the control group ($P = 0.87$).

Until now, six randomized trials [4, 12, 20, 28, 33], including the present trial, comparing surgery alone with postoperative adjuvant treatment with UFT, have been conducted. Among them, three trials demonstrated a

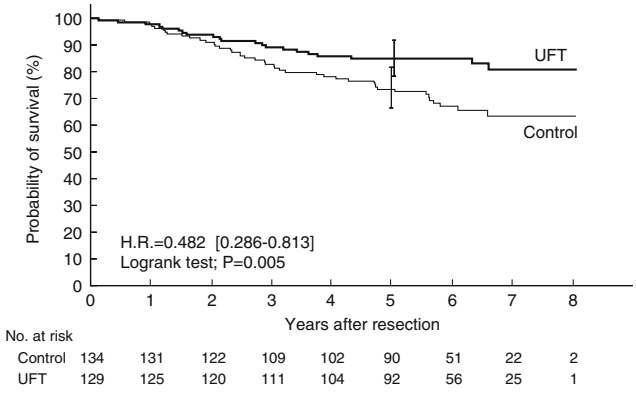

Fig. 3 Overall survival of all eligible patients with T2 disease ($n = 263$). *Error bars* represent the 95% confidence intervals. Reprinted with permission from the New England Journal of Medicine [15]. Copyright© 2004 Massachusetts Medical Society. All rights reserved

survival benefit for UFT [28, 33]. In addition, the results of a meta-analysis of those six trials demonstrated that adjuvant chemotherapy with UFT improved the overall survival (hazard ratio = 0.77, 95% CI: 0.63–0.94; $P = 0.01$) [8]. Whether the patients with stage II or III have a survival benefit from UFT treatment or whether the 1 year treatment is equivalent to the 2 year treatment remains unclear. However, patients with completely resected stage I disease, especially T2N0 adenocarcinoma, might be recommended to receive postoperative adjuvant chemotherapy with UFT based on the results of the present study.

Bestatin trial

Bestatin [(−)-*N*-[(2*S*,3*R*)-3-amino-2-hydroxy-4-phenyl-butyryl]-L-leucine] is an immunostimulator isolated from a culture filtrate of *Streptomyces olivoreticuli* that enhances the concanavalin A-induced activation of lymphocytes [14, 31]. This molecule inhibits the aminopeptidase N, aminopeptidase B, and leucine aminopeptidase of mammalian cells [16, 19]. Aminopeptidase N is identical to the myeloid differentiation antigen CD13 [1, 17] and is now considered to be a ubiquitous cell surface zinc aminopeptidase involved in the down-regulation of regulatory peptide signals [3, 24, 25, 27, 30]. Aminopeptidase N/CD13 is also reported to be involved in both tumor cell invasion [7, 26] and tumor angiogenesis [2, 23]. In addition, the expression of aminopeptidase N/CD13 in a tumor tissue is found to be an adverse prognostic factor in resected patients with lymph node-positive colon cancer [5].

In clinical studies, bestatin has demonstrated a prolongation of survival in adult acute nonlymphocytic leukemia in combination with chemotherapy [22, 32] and also an immunomodulatory effect in patients with lymphoma following autologous bone marrow transplantation [13]. Although a single institutional randomized clinical trial with bestatin as a postoperative adjuvant treatment in subjects with resected non-small cell lung cancer did not show any conclusive results, due to the small sample size, subset analysis indicated that bestatin could prolong survival in patients with completely resected pathological stage I squamous cell carcinoma [35]. This result prompted us to conduct a prospective, multi-center, randomized, double blind, placebo-controlled trial of bestatin as a postoperative adjuvant treatment for pathological stage I patients whose squamous cell carcinoma was completely resected.

From July 1992 through March 1995, 402 patients who had undergone a complete resection of pathologically documented stage I (T1–2N0M0) squamous cell carcinoma were enrolled in the trial. Two patients rescinded their informed consent before the start of treatment. The characteristics of patients who were randomly assigned to receive bestatin ($n = 202$) and placebo ($n = 198$) are shown in Table 3. There were no significant differences in the baseline characteristics of the patients. One capsule of either bestatin 30 mg or a placebo (vehicle without active drug) was orally administered after breakfast every day for 2 years postoperatively. The oral administration started within 1 week after the randomization.

There were few severe adverse reactions related to treatment and no significant difference in the incidence

Table 3 Patient characteristics in the bestatin trial

Characteristic	Bestatin ($n = 202$)	Placebo ($n = 198$)	P-value[a]
Age			
Median (years)	65	66	0.1828
Range (years)	41–76	45–75	
<65	83	66	0.1087
≥ 65	119	132	
Male sex	181	180	0.6600
ECOG performance status[b]			0.3906
0	117	125	
1	81	65	
2	4	8	
Tumor status			0.9655
Tis[c]	0	2	
1	99	95	
2	103	100	
3	0	1	
Location of the tumor			0.1724
Right upper lobe	44	64	
Right middle or lower lobe	53	51	
Right upper and middle lobe[d]	1	1	
Right upper and lower lobe[d]	0	2	
Left upper lobe	60	45	
Left lower lobe	42	34	
Left upper and lower lobe[d]	2	1	
Operation modality			0.4029
Lobectomy	197	189	
Pneumonectomy	5	8	
Segmentectomy	0	1	
Blood transfusion			0.9697
Done	36	35	
Not done	166	163	

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[a] All statistical tests were two-sided

[b] ECOG denotes Eastern Cooperative Oncology Group. Higher performance status numbers indicate greater impairment

[c] Carcinoma in situ

[d] The tumor was located between the lobes

Fig. 4 Overall survival of all eligible patients ($n = 400$). *Error bars* represent the 95% confidence intervals. Reprinted with permission from Oxford University Press [10]

of adverse reactions was observed between the groups, with the exception of anorexia. In the bestatin group, 18 patients had grade 1 anorexia, 6 had grade 2, and 5 had grade 3, while in the placebo group, 8 had grade 1, 1 had grade 2, and 4 had grade 3 anorexia. The incidence of anorexia of any grade was 15% (29/196) in the bestatin group and 7% (13/189) in the placebo group ($P = 0.0127$).

The median duration of follow-up for the surviving patients was 76 months (range, 58–92 months). As shown in Fig. 4, the 5 year survival rate was 81% (95% CI: 76–86%) in the bestatin group and 74% (95% CI: 68–80%) in the placebo group. The difference in survival was significant ($P = 0.033$ by the log-rank test, $P = 0.027$ by the Wilcoxon test: without a covariate adjustment).

In the multivariate analysis, the predetermined covariates were age, sex, ECOG performance status, T status, and blood transfusion, which are generally reported to affect prognosis [29, 34]. The covariates were selected according to the forward stepwise procedure ($P < 0.1$).

The selected covariates [*P*-value, comparison, relative risk (95% CI)] were as follows: age [$P = 0.003$, <65 vs ≥65 years, 1.92 (1.24–9.95)], performance status [$P = 0.010$, 0 vs 1 and 2, 1.63 (1.13–2.35)], blood transfusion [$P = 0.021$, no vs yes, 1.63 (1.08–2.47)], and sex [$P = 0.050$, female vs male, 2.28 (1.00–5.19)]. After adjustment, the result for the treatment group comparison [$P = 0.034$, bestatin vs placebo, 1.49 (1.03–2.16)] was almost the same as without any adjustment ($P = 0.033$).

In conclusion, the oral administration of bestatin as a postoperative adjuvant treatment was found to significantly prolong the survival of patients with completely resected stage I squamous cell carcinoma without any significant adverse events. However, to confirm the present conclusions, another phase III trial should be conducted.

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