A Phase II Trial of Oral Tegafur and Uracil plus Cisplatin in Patients with Inoperable Nonsmall Cell Lung Cancer

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Background. **The combination of uracil and tegafur in a 4:1 molar concentration (UFT) has a greater antitumor activity than 5-fluorouracil (5-FU) and tegafur. Because the combination of 5-FU and cisplatin has been proven to have a synergistic antitumor effect in many experimental and clinical studies, a Phase II study was conducted using the combination of UFT and cisplatin in patients with inoperable nonsmall cell lung cancer.**

Methods. **Thirty-one patients with measurable disease were entered into the study; all were evaluable for toxicity and response. Their median age was 61 years (range, 36–75 years). There were 13 patients with Stage III and 17 with Stage IV disease. Twenty-two (71%) patients had received no prior treatment. UFT (400 mg/m^2) was administered orally on days 1 through 21 and cisplatin (80 mg/m^2) was injected intravenously on day 8. This treatment was repeated every 4 weeks.**

Results. **The median number of treatment cycles was two (range, 1–4 cycles). There were 11 partial responses (35%; 95% confidence interval, 19%–52%). The median response time was 6 months (range, 3–13 months). The median survival time was 11 months (range, 4–27+ months) for Stage III and 8 months (range, 2–22 months) for Stage IV. This chemotherapy regimen was well tolerated. The hematologic toxicities, such as leukopenia and thrombocytopenia of grades 3 and 4, occurred in only 2 of 31 (6%) patients. Nonhematologic toxicities of grades 3 or 4 were not observed.**

Conclusions. **Oral UFT plus cisplatin administration demonstrated an activity comparable with that of other combinations based on cisplatin and an extremely low incidence of side effects. These observations suggest that this chemotherapy regimen is worthy of further investigation in a multi-institutional trial to determine the antitumor effect and the quality of life of patients. *Cancer* 1995;75:2677–80.**

Key words: UFT, cisplatin, inoperable nonsmall cell lung cancer, Phase II trial.

UFT (Taiho Pharmaceutical, Ltd., Tokyo, Japan) is a combination of uracil and tegafur in a 4:1 molar concentration. Tegafur (1-[2-tetrahydrofuryl]-5-fluorouracil) is a prodrug that is absorbed from the small intestine and is then metabolized in vivo to 5-fluorouracil (5-FU).[1] When compared with 5-FU and tegafur, UFT is reported to have a greater antitumor activity.[2] This potentiation is thought to be due to the inhibitory effect of uracil on the degradation of 5-FU by hepatic dihydropyrimidine dehydrogenase, which is the rate-limiting enzyme in 5-FU catabolism.[3] In addition, both animal and human studies have shown that the tumor levels of 5-FU achieved after the concomitant administration of uracil and tegafur in the above ratio are higher than levels in the peripheral blood and that the 5-FU level in the tumor tissue is also sustained for a longer period.[4,5]

The combination of cisplatin and 5-FU has been proven to have a synergistic antitumor effect in many experimental and clinical studies.[6–9] The antitumor activities of cisplatin and 5-FU are known to be dose- and time-dependent, respectively.[10] Therefore, the regimen using a bolus infusion of cisplatin and constant infusion of 5-FU is most preferred. In general, the duration of constant 5-FU infusion ranges from 3–5 days,[7–9] for which patients may require hospitalization. The quality of life of the patients is also hampered by constant infusions.

With these background, we conducted a Phase II trial combining the oral administration of UFT for 21

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days and a bolus infusion of cisplatin in patients with inoperable nonsmall cell lung cancer.

Patients and Methods

The patients were eligible for this study if they had either cytologically or histologically confirmed inoperable nonsmall cell lung cancer; measurable disease; age 75 years or younger; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; a leukocyte count of 4000/μl or greater; platelet count of 100,000/μl or greater; hemoglobin level of 9 g/dl or greater; serum bilirubin levels less than 1.5 mg/dl; serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels of twice the upper limit of normal or less; normal serum creatinine level; no evidence of any severe heart or pulmonary disease, and no active concomitant malignant disease. The staging was performed according to the new international staging system.[11] All the patients underwent computed tomography scans of the thorax and abdomen and isotope bone scan. Informed consent was obtained from all patients.

Uracil and tegafur (400 mg/m^2) in the form of 100 mg capsule (100 mg tegafur and 224 mg uracil) was given orally from days 1–21. The UFT dose was rounded up or down to the nearest 100 mg. If the capsule dose could not be divided equally, the higher dose was administered in the morning and the lower dose in the evening. In practice, most patients received 600 mg UFT per day (300 mg two times a day). Cisplatin (80 mg/m^2) was administered as a 90-minute infusion on day 8 when the patients received hydration of at least 2500 ml. The treatment was repeated every 4 weeks. At least two cycles of the treatment were given unless there was either unequivocal disease progression or toxicity.

A complete blood cell count, blood chemistry, and chest X-rays were performed once a week after the treatment began. The patients were evaluated for their response based on the standard World Health Organization criteria.[12] Toxicity from chemotherapy was graded according to the Japan Clinical Oncology Group.[13] The duration for the response was measured from the start of the treatment to disease progression. The survival curve from the start of the treatment was made using the Kaplan–Meier Method.

Results

Thirty-one patients were entered onto the study from February 1992 to November 1993. The median follow-up period was 20 months (range, 9–30 months). All patients were eligible. The characteristics of the patients are shown in Table 1. One patient who underwent a right pneumonectomy later developed metachronous Stage I lung cancer. The disease was judged to be inoperable due to his poor pulmonary function. One patient had Stage IIIA disease with an extranodal invasion of the ipsilateral mediastinal metastases. Therefore, 30 of 31 (97%) patients had advanced disease.

Table 1. Patient Characteristics

Characteristic	No. of patients	Percentage
No. of eligible patients	31	
Median age (range)	61 (36–75)	
Sex		
Male	23	74
Female	8	26
Stage of disease		
I	1	3
IIIA	1	3
IIIB	12	39
IV	17	55
PS (ECOG scale)		
0, 1	27	87
2	4	13
Histology		
Adenocarcinoma	15	48
Squamous cell carcinoma	15	48
Adenosquamous cell carcinoma	1	3
Prior treatment		
None	22	71
Chemotherapy with/without radiotherapy or surgery	6	19
Surgery or radiotherapy	3	10

PS: performance status; ECOG: Eastern Cooperative Oncology Group.

One to 4 cycles of the treatment were administered (1 cycle, 9 patients; 2 cycles, 14 patients; 3 cycles, 7 patients; 4 cycles, 1 patient). The response to the treatment was as follows: complete response, 0; partial response, 11; no change, 11; progressive disease, 9. The overall response rate was 35% (95% confidence interval: range, 19% to 52%). In 11 patients with partial response, six and five patients achieved at least a 50% tumor reduction after one cycle and two cycles, respectively. The responding patients were classified as follows: 6 (35%) of 17 Stage IV, 5 (36%) of 14 other stages; 6 (40%) of 15 squamous cell carcinomas, 5 (31%) of 16 other histologies; 4 (44%) of 9 patients with prior therapy, 7 (32%) of 22 without prior therapy. The median duration of the response was 6 months (range, 3 to 13 months).

Eight patients underwent thoracic irradiation after the combination chemotherapy. One patient in Stage IIIB with histologically confirmed contralateral supraclavicular lymph node metastasis who had received two cycles of the chemotherapy and achieved partial re-

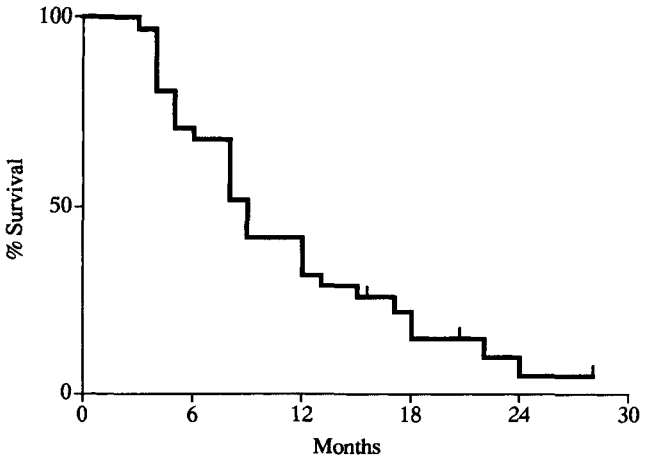

Figure 1. Survival; each tick mark represents a patient who is alive.

sponse underwent a left upper lobectomy with a dissection of the mediastinal and supraclavicular lymph nodes. The pathologic examination revealed only a microscopic residual tumor in the primary lesion. Figure 1 shows the survival curve of all 31 patients. The 1-year survival rate of these patients was 32%, whereas the median survival time was 8 months (range, 2–27+ months). Thirteen patients with Stage III disease had a 1-year survival rate of 31%, with a median survival time of 11 months (range, 4–27+ months) whereas 17 Stage IV patients had a 1-year survival rate of 29% and a median survival time of 8 months (range, 2–22 months).

The toxicities observed during the entire treatment of 31 patients are shown in Table 2. Leukopenia of grade 3 (1000–1900/μl) was observed in 2 (6%) patients. At the same time, these two patients had thrombocytopenia of grade 3 (25,000–49,000/μl) or grade 4 (<25,000/μl). Although no patient demonstrated grade 3 vomiting (vomiting of $\geqq$6 episodes in 24 hours), four patients could not take UFT for 1 to 7 days after the administration of cisplatin. No other toxicities, including cardiac, neurologic, and pulmonary toxicities, which are not listed in Table 2, were observed. There were also no treatment-related deaths.

Discussion

The combination of 5-FU and cisplatin has been shown to produce synergistic cytotoxicity in both in vitro studies and tumor-bearing animals.[14–16] However, the optimal order of administration of these drugs in combination therapy has yet to be determined. The sequence of cisplatin followed by 5-FU has been shown to be more cytotoxic than the reverse succession in in vitro studies,[14] whereas the sequence of 5-FU followed by cisplatin has been proven to have a greater antitumor activity than the opposite order of administration in tumor-bearing animals.[15,16] Therefore, in the present study, we designed a treatment regimen that is thought to be a compromise solution between conflicting experimental data; namely, a daily administration of UFT from day 1 to 21 and a bolus infusion of cisplatin on day 8.

The effect of cisplatin or UFT as a single agent on advanced nonsmall cell lung cancer is not satisfactory. The response rate of these patients to UFT and cisplatin is reported to be 6–8%[17,18] and 12–14%,[19] respectively. Although the results of the present trial cannot be directly compared with the above data, the response rate of 35% in the present trial indicates the combination of UFT and cisplatin may have a synergistic antitumor effect.

One of the advantages of this treatment is the extremely low incidence of toxicity. Hematologic toxicity, such as leukopenia and thrombocytopenia, was observed only in 6% of the patients. In addition, no severe nonhematologic toxicities occurred. These observations suggest that this treatment is suitable for outpatients and that the addition of another active drug against

Table 2. Toxicities According to the Japan Clinical Oncology Group

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Incidence of grade 3 or 4 toxicity (%)
Leukopenia	6	2	2	0	2 (6)
Anemia	6	7	3	0	3 (10)
Thrombocytopenia	4	0	1	1	2 (6)
Nausea/vomiting	7	24	0	—	0
Diarrhea	1	0	0	0	0
Stomatitis	2	0	0	0	0
Alopecia	5	0	—	—	0
Elevation of serum creatinine	0	1	0	0	0
Elevation of transaminase	2	1	0	0	0

nonsmall cell lung cancer is also feasible with this regimen.

Further studies on chemotherapy using oral UFT in various cancers are now underway.[20–23] Treatment with UFT alone and UFT plus leucovorin in advanced colorectal cancer has been reported to show moderate and significant antitumor activities, respectively.[20,21] In a randomized controlled study of postoperative adjuvant chemotherapy including UFT in nonsmall cell lung cancer patients, the chemotherapy group has been reported to prolong survival compared with the control group.[22] A recent study has demonstrated that oral UFT and cisplatin achieve a similar objective response rate to a constant infusion of 5-FU and cisplatin in advanced squamous head and neck cancer patients.[23] The present study also demonstrated that oral UFT and cisplatin has activity comparable with that of other combinations based on cisplatin. Even if we take into account only patients with Stage IV disease, this chemotherapy regimen is still considered to have a favorable activity (response rate of 36% and median survival time of 8 months). In addition to the extremely low incidence of side effects, another advantage of this regimen is that oral UFT administration spares the patients from the distress associated with a constant infusion of 5FU. In conclusion, we think that oral UFT and cisplatin treatment in inoperable nonsmall cell lung cancer is worthy of further investigation as a multi-institutional trial in terms of the antitumor effect and quality of life of patients.

References

1. Toide H, Akiyoshi H, Minato Y, Okuda H, Fujii S. Comparative studies on the metabolism of 2-(tetrahydrofuryl)-5-fluorouracil and 5-fluorouracil. *Gann* 1977;68:553–60.
2. Maehara Y, Kusumoto T, Kusumoto H, Anai H, Sugimachi K. UFT is more antineoplastic against gastric carcinoma than 5-fluorouracil, 1-(2-tetrahydrofuryl)-5-fluorouracil and 1-hexylcarbamoyl-5-fluorouracil. *Chemotherapy* 1988;34:484–9.
3. Pinedo HM, Peter FJ. Fluorouracil: biochemistry and pharmacology. *J Clin Oncol* 1988;6:1653–64.
4. Fujii S, Kitano S, Ikenaka K, Shirasaka T. Effect of coadministration of uracil or cytosin on the antitumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. *Gann* 1979;70:209–14.
5. Kimura K, Suga S, Shimaji T, Kitamura M, Kubo K, Suzuoki Y, et al. Clinical basis of chemotherapy for gastric cancer with uracil and 1-(2-tetrahydrofuryl)-5-fluorouracil. *Gastroenterologia Japonica* 1980;15:324–9.
6. Schabel FM Jr., Trader MW, Laster WR Jr., Corbett TH, Griswold DP Jr. Cis-Dichloro-diammineplatinum (II): combination chemotherapy and cross-resistance studies with tumors of mice. *Cancer Treat Rep* 1979;63:1459–73.
7. Decker DA, Drelichman A, Jacobs J, Hoschner J, Kinzie J, Loh JJ, et al. Adjuvant chemotherapy with cis-diamminedichloroplatinum II and 120-hour infusion 5-fluorouracil in stage III and IV squamous cell carcinoma of the head and neck. *Cancer* 1983;51:1353–5.
8. Kemeny N, Israel K, Niedzwiecki D, Chapman D, Botet J, Minsky B, et al. Randomized study of continuous infusion fluorouracil versus fluorouracil plus cisplatin in patients with metastatic colorectal cancer. *J Clin Oncol* 1990;8:313–8.
9. Richards F II, Perry DJ, Goutson M, Modeas C, Muchmore E, Rega V, et al. Chemotherapy with 5-Fluorouracil (5-FU) and cisplatin or 5-FU, cisplatin or 5-FU, cisplatin, and vinblastine for advanced non-small cell lung cancer: a randomized phase II study of the Cancer and Leukemia Group B. *Cancer* 1991;67:2974–9.
10. Shirasaka T, Shimamoto Y, Ohshima H, Saito H, Fukusima M. Metabolic basis of the synergistic antitumor activities of 5-fluorouracil and cisplatin in rodent tumor models in vivo. *Cancer Chemother Pharmacol* 1993;32:167–72.
11. Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89:225S–33S.
12. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publ. No. 48. World Health Organization, Geneva, Switzerland, 1979.
13. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 1993;23:250–7.
14. Scanlon KJ, Newman EM, Lu Y, Priest DG. Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. *Proc Natl Acad Sci USA* 1986;83:8923–5.
15. Pratesi G, Gianni L, Manzotti C, Zunino F. Sequence dependence of the antitumor and toxic effects of 5-fluorouracil and cis-diamminedichloroplatinum combination on primary colon tumors in mice. *Cancer Chemother Pharmacol* 1988;21:237–40.
16. Kuroki M, Nakano S, Mitsugi K, Ichinose I, Anzai K, Nakamura M, et al. In vivo comparative therapeutic study of optimal administration of 5-fluorouracil and cisplatin using a newly established HST-1 human squamous-carcinoma cell line. *Cancer Chemother Pharmacol* 1992;29:273–6.
17. Keicho N, Saijo N, Shinkai T, Eguchi K, Sasaki Y, Tamura 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.
18. Shimizu E, Kimura K, Sone S, Inoue I, Nakamura Y, Noda Y, et al. A phase II study of UFT for non-small cell lung cancer [in Japanese]. *Jpn J Cancer Chemother* 1986;13:2970–3.
19. Gandara DR, Crowley J, Livingston RB, Perez EA, Taylor CW, Weiss G, et al. Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a phase III study of the Southwest Oncology Group. *J Clin Oncol* 1993;11:873–8.
20. Malik STA, Talbot D, Clarke PI, Osborne R, Reznek R, Wrigley PFM, et al. Phase II trial of UFT in advanced colorectal and gastric cancer. *Br J Cancer* 1990;62:1023–5.
21. Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugarman SM, Patt YZ, et al. Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J Clin Oncol* 1994;12:2296–300.
22. Wada H, Hitomi S, Teramatsu T. Postoperative non-small cell lung cancer: a prospective randomized trial of cisplatin-vindesine-UFT vs UFT alone vs control. *Proc Am Soc Clin Oncol* 1994;13:328 (abstract 1084).
23. Valverde JJ, Gonzalez JL, Dominguez S, Lopez PM, Alonso MC, Adrover E, et al. Neoadjuvant chemotherapy with cisplatin and 5 fluoro-uracil versus cisplatin and ftorafur-uracil (UFT) in advanced squamous head and neck cancer. *Proc Am Soc Clin Oncol* 1993;12:281 (abstract 909).