Int J Clin Oncol (2001) 6:236–241

ORIGINAL ARTICLE

**Kiyoyuki Furuse · Masaaki Kawahara · Koichi Hasegawa
Shoji Kudoh · Minoru Takada · Takahiko Sugiura
Yukito Ichinose · Masahiro Fukuoka · Yasuo Ohashi
Hisanobu Niitani, for the S-1 Cooperative Study Group
(Lung Cancer Working Group)**

Early phase II study of S-1, a new oral fluoropyrimidine, for advanced non-small-cell lung cancer

Received: February 13, 2001 / Accepted: August 28, 2001

Abstract
Background. The efficacy and safety of S-1, a new oral fluoropyrimidine, were evaluated in patients with non-small-cell lung cancer (NSCLC). The objective of this study was to determine whether the drug should be investigated in a late phase II study.
Methods. Each treatment course consisted of an oral dose of S-1, 50 mg/body or 75 mg/body, twice a day for 28 days, followed by a 2-week washout period.
Results. Fifty-six eligible patients were enrolled. Five of the 40 previously untreated patients (12.5%; 90% confidence interval, 6.2%–23.5%) showed a partial response (PR), and no tumor response was observed in the 16 previously treated patients. The median survival duration in all eligible patients was 8.4 months, with a 1-year survival rate of 27.3%. The incidences of grade 3 or more severe adverse effects were: anemia, 5.4%; leukopenia, 5.4%; neutropenia, 5.4%; thrombocytopenia, 1.8%; anorexia, 3.6%; diarrhea, 3.6%; and general fatigue, 5.4%. These effects disappeared after cessation of the drug or appropriate treatment. One patient died as a result of aggravated interstitial pneumonitis, but the relationship of this event to S-1 was not clear.
Conclusion. S-1 showed modest activity with mild toxicity in the treatment of non-small-cell lung cancer. Based on this result, we will progress to the next stage of a late phase II study for advanced NSCLC, and a phase II study of S-1 and cisplatin for advanced gastric cancer. Final results will be reported as they are obtained.

Key words S-1 · Non-small-cell lung cancer (NSCLC) · Early phase II study

K. Furuse (✉)
Division of Respiratory Diseases, Health Insurance Union Osaka Central Hospital, 3-3-17 Niwashirodai, Sakai, Osaka 590-0133, Japan
Tel. +81-722-99-1460; Fax +81-722-99-1461
e-mail: ha7k-frs@asahi-net.or.jp

M. Kawahara
Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, Osaka, Japan

K. Hasegawa
Department of Internal Medicine, Tsuboi Hospital, Fukushima, Japan

S. Kudoh
Department of Respiratory Diseases, Nippon Medical School, Tokyo, Japan

M. Takada
Second Department of Internal Medicine, Osaka Prefectural Habikino Hospital, Osaka, Japan

T. Sugiura
Department of Pulmonary Diseases, Aichi Cancer Center, Nagoya, Japan

Y. Ichinose
Department of Chest Surgery, National Kyushu Cancer Center, Fukuoka, Japan

M. Fukuoka
Department of Respiratory Diseases, Osaka City General Hospital, Osaka, Japan

Y. Ohashi
Department of Biostatistics, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan

H. Niitani
The Tokyo Cooperative Oncology Group, Tokyo, Japan

Introduction

It has been predicted that lung cancer would be the leading cause of death from cancer in both males and females in Japan by the year 2000. Currently, non-small-cell lung cancer (NSCLC) accounts for approximately 75%–80% of the incidence of and mortality from all lung cancers. While surgical resection offers the best chance for long-term survival in patients with stage I or II disease, approximately two-thirds of NSCLC patients will not be candidates for resection because of the presence of either locally advanced tumors or distant metastasis.[1] The prognosis of patients with metastatic disease is poor, with a median survival of 5 to 12 months.[2] Fewer than 5% of these patients are long-term survivors (i.e., longer than 2 years),[3] and only systemic treatment can increase this percentage.

S-1 is a new oral fluoropyrimidine anticancer agent, produced by combining tegafur (FT),[4] a prodrug of 5-fluorouracil (5-FU), with 5-chloro-2, 4-dihydroxypyrimidine (CDHP)[5] and potassium oxonate (Oxo)[6] at a molar ration of 1:0.4:1.

CDHP effectively inhibits the decomposition of 5-FU by dihydrouracil dehydrogenase and provides a high and sustained blood concentration of 5-FU comparable to that of a continuous intravenous drip infusion.[7] Oxo specifically inhibits the phosphorylation of 5-FU in the gastrointestinal mucosa and reduces the side effects of mucosal damage, such as diarrhea and stomatitis. The high anticancer activity of this drug was confirmed in a study of animals with transplanted human tumors.[8] Also, this drug is reportedly effective in the treatment of gastric, breast, and head and neck cancers.[9–11]

According to a phase I clinical trial, the dose-limiting factor (DLF) for S-1 is myelosuppression, with the main manifestation being leukopenia.[12] It was also suggested that the recommended dosage in early phase II clinical trials be 75 mg/body (the FT dose) twice a day for 28 consecutive days, followed by a 2-week washout period.[12] Here, we report on a multicenter trial assessing the efficacy of S-1 against NSCLC that was performed at 15 institutions between March 1994 and March 1996.

Patients and methods

Eligibility criteria

Eligibility criteria included the following: cytologic or histologic diagnosis of NSCLC; unresectable stage IIIB or IV without previous treatment or with a history of two courses or less of chemotherapy, but no thoracic radiotherapy; measurable or assessable lesions; between 20 and 80 years of age, performance status less than 2 on the Eastern Cooperative Oncology Group (ECOG) scale; adequate renal (serum creatinine within normal range), liver (bilirubin, $\leqq$1.5 mg/dl; aspartate aminotransferase [AST], alamine transferase [ALT], and alkaline phosphatase [Al-p], $<$ two times upper limit of normal), bone marrow (leukocyte count, $\geqq$4000/μl; platelet count, $\geqq$100000/μl), and more than 3-month survival expectancy. Patients had no previous drug allergy, severe physical complications, symptoms caused by brain metastasis, or concomitant malignancy, were not pregnant/nursing, and had no other medical problems. Patients gave their informed consent for participation in the trial. The study was approved by the institutional review boards of the participating institutions. (see Appendix for list).

Treatment schedule

Each chemotherapy course consisted of 75 mg/body twice a day at the planned initial dose of S-1 after breakfast and dinner for 28 consecutive days, followed by a rest period of 2 weeks. The maximum number of courses was four. If leukopenia of grade 3 or more occurred, chemotherapy was discontinued and was withheld until the leukocyte count recovered to at least 3000/μl. Suspension of chemotherapy was allowed for a period of up to 4 weeks.

Assessment of response

Before being registered for the study, all patients gave a full medical history and received complete physical and bronchoscopic examinations; bone scintigraphy; chest X-ray; computed tomographic scan of chest, abdomen, and brain; routine blood chemistries; blood cell count; urinalysis, and electrocardiogram (ECG). For the assessment of response and toxicity in each patient, a complete clinical record and physical examination was obtained. In addition, routine blood chemistry examinations, including AST, ALT, A1-P, lactic dehydrogenase (LDH), bilirubin, serum creatinine, and blood urea nitrogen, and a complete blood cell count and urinalysis, were repeated once per week during the study.

Evaluation of response was based on the criteria of therapeutic effects for primary and metastatic lung cancer established by the Japan Lung Cancer Society.[13] Evaluation of toxicity was based on the criteria of chemotherapeutic effects for solid tumors established by the Japan Society for Cancer Therapy.[14] Both sets of criteria were modified on the basis of World Health Organization (WHO) criteria.[15] Assessment categories for response were as follows: a complete response (CR) was defined as the disappearance of any evidence of tumor for at least 4 weeks. A partial response (PR) was defined as a 50% or more reduction in the sum of the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. No change (NC) was defined as a less than 50% reduction or a less than 25% increase in the products of the greatest perpendicular diameters of all lesions without evidence of new lesions for 4 weeks. Progression of disease (PD) was defined as an increase of greater than 25% or the appearance of new lesions. The response duration was measured from the start of chemotherapy to disease progression.

Extramural reviewers verified eligibility criteria, staging, and toxicity. They also reviewed original X-rays to evaluate each patient. The efficacy of the drug was judged by external reviewers. S-1 was provided by Taiho Pharmaceutical (Tokyo, Japan).

Statistical methods

The efficacy of the drug in untreated patients was evaluated using the 90% confidence interval of response rate; the threshold rate was defined as 5% and the expected rate was set as 20%. When the number of eligible patients reached 20, patient enrollment was discontinued and an interim analysis was performed. If the lower limit of the 90% confidence interval exceeded the 5% threshold (efficacy in 4 or more of the 20 previously untreated eligible patients) the drug was judged to be effective. If the upper limit of the 90% confidence interval did not exceed the expected rate of 20% (no objective response in the 20 previously untreated

Table 1. Patient characteristics

		No. of patients
Mean age (years; median)	68 (69)	
Age (years; range)	36–78	
Sex; male/female	41/15 (30/10)	
ECOG performance status scale		
0		9 (5)
1		38 (30)
2		9 (5)
Stage		
IIIB		15 (12)
IV		41 (28)
Histology		
Adenocarcinoma		37 (26)
Squamous cell carcinoma		14 (10)
Large-cell carcinoma		3 (3)
Adenosquamous carcinoma		2 (1)

Numbers in parentheses show numbers of untreated patients (total, $n = 40$)
ECOG, Eastern Cooperative Oncology Group

eligible patients), the drug was judged to be ineffective and the study was terminated. If response was confirmed in 1–3 of 20 previously untreated eligible patients, the study was continued until the number of eligible patients reached 35. The efficacy in previously treated patients was evaluated in the same manner. The number of patients in each category was set at 20. Survival was calculated from the date of start of chemotherapy, using the Kaplan-Meier method.

Results

Patients and demographic characteristics

We observed one PR within the first 20 previously treated patients in the interim analysis. Accordingly, we decided to expand the study, and previously untreated patients were enrolled until the termination of the study. Of the 16 previously treated patients in the interim analysis, none responded, and enrollment was closed.

In total, 58 patients were enrolled in this study. However, 2 patients were excluded: 1 had received radiation therapy for metastases and the other was confirmed to have mesothelioma. Table 1 shows the demographic details of the 56 eligible patients. Forty-one patients (30 untreated) were male and 15 (10 untreated) female. Age ranged from 36 to 78 years. The overall median age was 68 years, and 69 years in untreated patients. The histological classification of lung cancer was adenocarcinoma in 37 (26, untreated), squamous cell carcinoma in 14 (10, untreated), adenosquamous carcinoma in 2 (1, untreated) and large-cell carcinoma in 3 (3, untreated). The clinical stage was IIIB in 15 (12, untreated) and IV in 41 (28, untreated).

Treatment response

Of the 40 untreated eligible patients, 5 (12.5%; 90% confidence interval, 6.2%–23.5%) achieved a PR, 19 showed NC, 13 had PD, and 3 could not be evaluated for response. In terms of histological classification, PR was noted in 3 of the 26 patients with adenocarcinomas, 1 of the 10 patients with squamous cell carcinomas, and 1 of the 3 patients with large-cell carcinomas. In terms of clinical stage, PR was noted in 8.3% (1/12) of patients in stage IIIB and in 14.3% (4/28) of patients in stage IV. No tumor response was observed in the 16 previously treated patients.

The period from the start of therapy to the achievement of PR varied from 24 to 72 days (median, 32 days). The response duration varied from 16.3 to 38.4+ weeks (median, 21.4+ weeks).

Treatment delivery

We began oral administration of the initial dose of 75 mg/body of S-1 twice a day; however, a grade 1 or 2 skin eruption occurred in 4 of the first 6 patients (66.7%) receiving the dose, and we reduced the initial dose to 50 mg/body twice a day. Subsequently, of 50 patients who were treated with the initial dose of 50 mg/body, only 7 patients (14%) had a grade 1 or 2 skin eruption.

In total, 117 cycles of S-1 were administered orally, consisting of 102 cycles of 50 mg/body and 15 cycles of 75 mg/body. The median S-1 dose of 50 mg/body constituted a cumulative dose of 2800 mg, ranging from 600 to 44650 mg, and for 75 mg/body, the cumulative dose was 1800 mg, ranging from 225 to 9225 mg.

Survival

At the median follow-up time of 30.9 weeks, the projected median survival duration was 8.4 months, with a 1-year survival rate of 27.3% for the 56 eligible patients, and 9.5 months, with a 1-year survival rate of 26.7% in previously untreated patients (Fig. 1).

Toxicity

The safety of the drug was evaluated in the 56 eligible patients. Table 2 shows the major toxicities identified. Anemia, leukopenia, neutropenia, thrombocytopenia, increases in AST, ALT, and LDH, stomatitis, anorexia, diarrhea, nausea, vomiting, skin rash, and general fatigue were noted. The incidences of grade 3 or more severe adverse effects were: anemia, 5.4% (3/56); leukopenia, 5.4% (3/56); neutropenia, 5.4% (3/56); thrombocytopenia, 1.8% (1/56); anorexia, 3.6% (2/56); diarrhea, 3.6% (2/56), and general fatigue, 5.4% (3/56). These adverse effects disappeared after cessation of the drug or appropriate treatment of the effects. One patient died of aggravated interstitial pneumonitis. He had a history of this ailment, but it had been stable prior to the treatment of S-1. However, the treatment was terminated because of the progression of cancer after one course of chemotherapy. Subsequently, the interstitial pneumonitis was aggravated, and he died 44 days after the last administration of S-1. The relationship of this event to

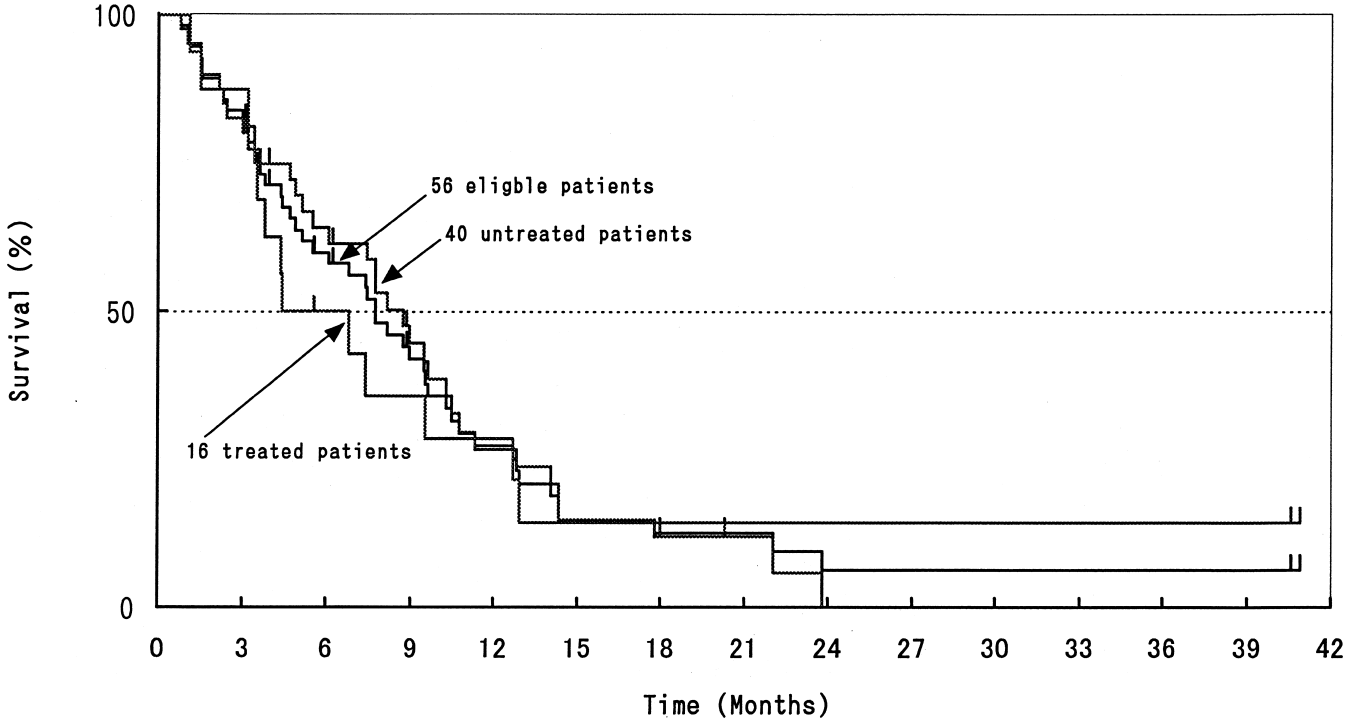

Fig. 1. Overall survival. *Untreated*, Previously untreated; *treated*, previously treated

Table 2. Toxicity in 56 eligible patients

Toxicity	Grade				Incidence of grade 3 or more (%)
	1	2	3	4	
Leukopenia	7	6	3	0	5.4
Neutropenia	8	6	3	0	5.4
Anemia	3	10	3	0	5.4
Thrombocytopenia	3	0	1	0	1.8
AST[a]	7	0	0	0	0
ALT[a]	4	2	0	0	0
LDH[a]	13	3	0	0	0
General fatigue	9	2	2	1	5.4
Diarrhea	6	1	1	1	3.6
Anorexia	12	7	2	0	3.6
Stomatitis	4	3	0	0	0
Skin rash	9	2	0	0	0
Nausea/vomiting	9	3	0	0	0

[a] Increases in levels of AST, ALT, and LDH

S-1 was not clear. No other irreversible, severe, or unexpected adverse effects were noted.

Discussion

Orally formulated chemotherapy represents a potential major advance in patient convenience, especially in terms of the patient's quality of life, and the cost-effectiveness.[16] In combination with other anticancer drugs, 5-FU has been widely used in the treatment of various solid cancers, including NSCLC.[17,18] However, 5-FU is rapidly metabolized to 2-fluoro-beta-alanine, mostly in the liver by dihydrouracil dehydrogenase, and excreted in urine. Various 5-FU derivatives, such as tegafur,[19,20] tegafur plus uracil (UFT), 5′-deoxy-5-fluorouridine (5′DFUR),[21,22] and emitefur (BOF-A2),[23] have been developed with the aim of achieving greater anticancer effects by the inhibition of 5-FU decomposition or by achieving a high blood concentration of 5-FU. While BOF-A2 has demonstrated a response rate of 18%, 5′DFUR and UFT have produced much lower response rates (0–6%).[21,22] S-1, as well as BOF-A2, can produce a high interstitial 5-FU concentration owing to its markedly enhanced inhibition of 5-FU decomposition by dihydrouracil dehydrogenase.[24]

This phase I clinical trial suggested the DLF of this drug to be myelosuppression, with the main manifestation being leukopenia. It was also suggested that the recommended dosage in an early phase II clinical trial would be 75 mg/body (the FT dose) twice a day for 28 consecutive days, followed by a 2-week washout.

The response rate in the early phase II study demonstrated marginal activity for previously untreated patients with stage IIIB and IV NSCLC (12.5%, with a 90% confidence interval of 6.2%–23.5%). Also, the median survival time was 9.5 months, with a 1-year survival rate of 26.7%. The major toxicities recognized in this study were anemia, leukopenia, neutropenia, thrombocytopenia, anorexia, diarrhea, and general fatigue, although the incidences and extents of these adverse effects were clinically negligible.

The combination of 5-FU and cisplatin has been shown to produce synergistic cytotoxicity in both in-vitro studies and tumor-bearing animals.[18,25–27] The response rates for

UFT or cisplatin as single agents in the treatment of NSCLC were reported to be 6%–8%[28] and 12%–14%,[29] respectively. However, in a phase II trial of combined UFT and cisplatin chemotherapy for previously untreated NSCLC, the response rate was 35%,[30] suggesting that these two agents have a synergistic effect. Moreover, in a randomized trial of postoperative adjuvant chemotherapy, including UFT, for NSCLC, chemotherapy with UFT alone or cisplatin/vindesine plus UFT yielded significantly better survival than surgery alone.[31]

We started at the initial dose of 75 mg/body of S-1 twice a day in this study. After 6 patients had received this dose, 4 (66.7%) had grade 1 or 2 skin eruptions. Therefore, we reduced the initial dose of S-1 to 50 mg/body twice a day. Subsequently, of the 50 patients who were treated with this dose, only 14% (7/50) had a grade 1 or 2 skin eruption. The study was terminated without any major problems.

Based on these results, we recommended that, in a late phase II study for advanced NSCLC and a phase II study of S-1 combined with cisplatin for advanced gastric cancer, the appropriate initial dose of S-1 should be 40 mg/m^2 twice a day. The preliminary results of these two studies were presented at the thirty-sixth and thirty-seventh American Society of Clinical Oncology (ASCO) meetings, respectively (held at New Orleans in May 2000 and at San Francisco in May 2001), and currently we are awaiting the final results of these two studies.[32,33]

Acknowledgments This study was supported by the Taiho Pharmaceutical Company, Ltd., Tokyo, Japan. Also, we thank Mr. Hideo Yamashita for data collection and Mr. Louis Garguilo for correcting our English manuscript.

Appendix

Participating institutions

The following institutions and specialists from the S-1 Cooperative Study Group took part in this research: Department of Radiology, Hyogo Medical Center for Adult Diseases (Yoshiki Takada); Department of Internal Medicine, National Shikoku Cancer Center (Masafumi Fujii); Department of Internal Medicine, Niigata Cancer Center Hospital (Akira Yokoyama); Department of Internal Medicine, Sendai Kosei Hospital (Yushi Nakai); Clinic of Surgery, Chest Diseases Research Institute, Kyoto University (Shigeki Hitomi); Second Department of Internal Medicine, Hiroshima University School of Medicine; (Michio Yamakido).

References

1. Ihde DC, Minna JD (1991) Non-small cell lung cancer. Biology, diagnosis and staging. Curr Probl Cancer 15:61–104
2. Ginsberg RJ, Kris MG, Armstrong JG (1993) Cancer of the lung. In: DeVita VT, Hellman S, Rosenberg SA (eds) Cancer, principles and practice of oncology, 4th edn. J.B. Lippincott, Philadelphia, pp 673–723
3. Finkelstein DM, Ettinger DS, Ruckdeschel JC (1986) Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 4:702–709
4. Shirasaka T, Shimamoto Y, Ohshimo H, et al. (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anti-Cancer Drugs 7:548–557
5. Tatsumi K, Fukushima M, Shirasaka T, et al. (1987) Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. Jpn J Cancer Res 78:748–755
6. Shirasaka T, Shimamoto Y, Fukushima M (1993) Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 53:4004–4009
7. Lokich JJ, Ahlgren JD, Gullo JJ, et al. (1989) A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol 7:425–432
8. Shirasaka T, Nakano K, Takechi T, et al. (1996) Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. Cancer Res 56:2602–2606
9. Horikoshi N, Mitachi Y, Sakata Y, et al. (1996) S-1, new oral fluoropyrimidine is very active in patients with advanced gastric cancer (early phase II study) (abstract). Proc Am Soc Clin Oncol 15:206
10. Taguchi T, Morimoto K, Horikoshi N, et al. (1998) Early phase II study of S-1 in patients with breast cancer. Jpn J Cancer Chemother 25:1035–1043
11. Inuyama Y, Kida A, Tsukuda M, et al. (1998) Early phase II study of S-1 in patients with advanced head and neck cancer. Jpn J Cancer Chemother 25:1151–1158
12. Taguchi T, Inuyama Y, Kanamaru R, et al. (1997) Phase I study of S-1. Jpn J Cancer Chemother 24:2253–2264
13. The Japan Lung Cancer Society (1987) Criteria of therapeutic effects for primary and metastatic lung cancer. In: Niitani H (ed) General rules for clinical and pathological recording of lung cancer, 3rd edn. Tokyo, Kanehara, pp 119–130
14. Furue H, Hara Y, Imamura Y, et al. (1986) Criteria of chemotherapeutic effects for solid cancer. J Jpn Soc Cancer Ther 21:943–953
15. World Health Organization (1979) WHO handbook for reporting results of cancer treatment. WHO Offset Publication No. 48, Geneva, Switzerland
16. DeMario MD, Ratain MJ (1998) Oral chemotherapy: rationale and future directions. J Clin Oncol 16:2557–2567
17. Weiden PL, Einstein AB, Rudolph RH (1985) Cisplatin bolus and 5-FU infusion chemotherapy for non-small cell lung cancer. Cancer Treat Rep 69:1253–1255
18. Richards FII, Perry DJ, Goutsou M, et al. (1991) Chemotherapy with 5-fluorouracil (5-FU) and 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 67:2974–2979
19. Valdivieso M, Bodey GP, Gottlieb JA, et al. (1976) Clinical evaluation of ftorafur (pyrimidine-deoxyribose N_1-2′-furanidyl-5-fluorouracil). Cancer Res 36:1821–1824
20. Ansfield FJ, Kallas GJ, Singson JP (1983) Phase I–II studies of oral tegafur (ftorafur). J Clin Oncol 1:107–110
21. Hara Y (1984) 5′-Deoxy-5-fluorouridine enzymatic activation from the masked compound to 5-fluorouracil in human malignant tissues. Jpn J Cancer Chemother 11:2133–2143
22. Niitani H, Kimura K, Saito T, et al. (1985) Phase II study of 5′-deoxy-5-fluorouridine (5′-DFUR) on patients with malignant cancer – multi-institutional cooperative study. Jpn J Cancer Chemother 12:2044–2051
23. Fujii S, Fukushima M, Shimamoto Y, et al. (1989) Antitumor activity of BOF-A2, a new 5-fluorouracil derivative. Jpn J Cancer Res 80:173–181
24. Nakai Y, Furuse K, Ohta M, et al. (1994) Efficacy of a new 5-fluorouracil derivative, BOF-A2, in advanced non-small cell lung cancer. Acta Oncol 33:523–526
25. Schabel FM Jr, Trader MW, Laster WR Jr, et al. (1979) Cis-Dichlorodiammineplatinum (II): combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 63:1459–1473
26. Decker DA, Drelichman A, Jacobs J, et al. (1983) Adjuvant chemotherapy with cis-diamminodichloroplatinum II and 120-h

infusion 5-fluorouracil in stage III and IV squamous cell carcinoma of the head and neck. Cancer 51:1353–1355
27. Kemeny N, Israel K, Niedzwiecki D, et al. (1990) Randomized study of continuous infusion fluorouracil versus fluorouracil plus cisplatin in patients with metastatic colorectal cancer. J Clin Oncol 8:313–318
28. Keicho N, Saijo N, Shinkai T, et al. (1986) Phase II study of UFT in patients with advanced non-small cell lung cancer. Jpn J Clin Oncol 16:143–146
29. Gandara DR, Crowley J, Livingston RB, et al. (1993) Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a phase III study of the Southwest Oncology Group. J Clin Oncol 11:873–878
30. Ichinose Y, Takanashi N, Yano T, et al. (1995) A phase II trial of oral tegafur and uracil plus cisplatin in patients with inoperable non-small cell lung cancer. Cancer 75:2677–2680
31. Wada H, Hitomi S, Teramatsu T (1996) Adjuvant chemotherapy after complete resection in non-small cell lung cancer. West Japan Study Group for Lung Cancer Surgery. J Clin Oncol 14:1048–1054
32. Niitani H, Kawahara M, Segawa Y, et al. (2000) Activity of S-1 in patients with non-small cell lung cancer. Results from a phase II Study (abstract). Proc Am Soc Clin Oncol 19:1995
33. Ohtsu A, Boku N, Nagashima Y, et al. (2001) A phaseI/II study of S-1 plus cisplatin (CDDP) in patients with advanced gastric cancer (AGC) (abstract). Proc Am Soc Clin Oncol 20:656