Phase I trial of oral S-1 plus gemcitabine in elderly patients with nonsmall cell lung cancer

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We conducted a phase I study to determine the maximum tolerated dose, the recommended dose and the safety profile of S-1 and gemcitabine combination regimen in the treatment of elderly patients (≥ 70 years) with advanced nonsmall cell lung cancer (NSCLC). Chemotherapy-naive patients with advanced NSCLC were treated with S-1 and gemcitabine. S-1 was administered orally twice daily for 14 days and gemcitabine on days 1 and 15 of each cycle, and this was repeated every 4 weeks. Doses of each drug were planned as follows: level 1, 800/60; level 2, 1000/60; level 3, 1000/70; and level 4, 1000/80 [gemcitabine (mg/m^2/day)/S-1 (mg/m^2/day)]. The dose-limiting toxicity (DLT) of the regimen was assessed during the first chemotherapy cycle. Sixteen patients were enrolled in this study. The main grade 3 toxicities observed during the first cycle were neutropenia (43.7%), leukopenia (18.7%), and hyperglycemia. One of six patients in level 3 had DLT. Although no patients in level 4 experienced DLT, this level was considered the maximum tolerated dose. Level 4 was selected as the recommended dose. Objective responses were seen in four patients (response rate, 42.9%). The combination of S-1 plus gemcitabine is a feasible and well-tolerated regimen for the treatment of elderly patients with advanced NSCLC. *Anti-Cancer Drugs* 19:289–294

Anti-Cancer Drugs 2008, **19**:289–294

Keywords: elderly, gemcitabine, nonsmall cell lung cancer, phase I study, S-1

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Received 9 October 2007 **Revised form accepted** 1 November 2007

Introduction

Nonsmall cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. Most patients present with locally advanced stage III or metastatic stage IV disease. A meta-analysis of 52 randomized trials indicated a significant, but modest survival advantage for patients treated with cisplatin-containing regimens, compared with best supportive care alone [1]. Although the median age of patients with newly diagnosed NSCLC participating in clinical trials is 60–62 years, more than 50% of diagnoses are made in patients aged more than 65 years, and 30–40% are made in patients more than 70 years old [2]. Elderly individuals have been underrepresented in such clinical trials, making it difficult to evaluate the efficacy and safety of current treatment options in this patient population [3]. Physicians tend to believe that aged patients often have poor tolerance for chemotherapy, and there is the potential to undertreat elderly patients because of the fear of excessive toxicity [4]. Thus, it is important to establish a feasible treatment regimen for elderly patients with NSCLC.

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral anticancer agent composed of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo), in a molar ratio of 1 : 0.4 : 1 [5]. FT, a prodrug of 5-fluorouracil (5-FU), is gradually converted to 5-FU and is rapidly catabolized by dihydropyrimidine dehydrogenase in the liver. CDHP is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting dihydropyrimidine dehydrogenase [6]. When combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations, both in plasma and in tumors. In addition, it has been suggested that CDHP has the potential to enhance the antitumor activity of 5-FU against subcutaneous tumors in nude mice [7]. Oxo is an agent that decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase. Oxo preferentially localizes in the gut rather than in the tumor and has a potential biochemical effect on the enzyme pyrimidine phosphoribosyl transferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects [8].

In a phase II study of S-1, which was orally administered at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced NSCLC

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patients without prior chemotherapy, the response rate was 22% and the median survival time was 10.2 months. The incidence of grade 3 or 4 toxicity was low [9]. Additionally, a response rate of 47%, median survival time of 11 months, and 1-year survival rate of 45% were reported in the phase II study of 55 advanced NSCLC patients when S-1 was combined with cisplatin [10]. A recent clinical trial revealed that combination chemotherapy of S-1 plus carboplatin is a feasible and well-tolerated regimen for the treatment of patients with advanced NSCLC [11].

Gemcitabine, an anticancer drug structurally resembling cytosine arabinoside, has been shown to have high antitumor activity and minimal adverse effects [12]. Therefore, it is reasonable to assume that gemcitabine could be better tolerated in older patients or patients with poor performance status (PS). Ichinose *et al.* [13,14] showed that combination chemotherapy of gemcitabine plus UFT demonstrated a promising effectiveness and acceptable toxicity in patients with advanced NSCLC. Recently, the combination chemotherapy with gemcitabine plus oral S-1 was shown to be well-tolerated and promising in patients with advanced pancreatic cancer [15–17]. Thus, both gemcitabine and S-1 are antimetabolites with minimal adverse effects could be expected to provide a better quality of life. These two drugs inhibit DNA synthesis via different pathway, that is, DNA chain termination and thymidylate synthase inhibition, respectively. We can therefore expect synergistic effects when they are used in combination.

Against this background, we conducted a phase I study of S-1 plus gemcitabine in elderly patients with advanced NSCLC to determine the maximum tolerated dose (MTD) to be investigated further in a phase II study.

Patients and methods

Patient eligibility

Eligible patients were required to have histologically and/or cytologically proven unresectable stage IIIB or IV NSCLC; no previous chemotherapy or radiotherapy; a PS of 0–1 on the Eastern Cooperative Oncology Group; an age more than 70 years; a life expectancy of 12 weeks or more; adequate bone marrow reserve (leukocyte count $\geq 4000/mm^3$, neutrophil count $\geq 2000/mm^3$, platelet count $\geq 100\,000/mm^3$, and hemoglobin ≥ 10 g/dl); normal liver function (total serum bilirubin ≤ 1.5 mg/dl, and aspartate transaminase, alanine transaminase less than twice the upper limit of the normal range), normal renal function (normal serum creatinine and blood urea nitrogen levels), and pulmonary function ($PaO_2 \geq 60$ Torr). Patients with concomitant malignancy, central nervous system metastases, active infectious diseases, or other serious medical problems were ineligible. The local ethics committee approved the study and written informed consent was obtained from all patients.

Clinical study design

This was an open-label, single-center, single-arm, dose-escalating phase I study. S-1 was administered orally twice daily after a meal for 14 consecutive days, followed by a 2-week break. Each capsule of S-1 contained 20 or 25 mg of FT. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. Gemcitabine was administered as a 30-min intravenous infusion on days 1 and 15 of each cycle. The cycle was repeated every 4 weeks. The dose of each drug in this study was planned as follows: level 1 was S-1 60 mg/m^2/day and gemcitabine 800 mg/m^2, level 2 was S-1 60 mg/m^2/day and gemcitabine 1000 mg/m^2, level 3 was S-1 70 mg/m^2/day and gemcitabine 1000 mg/m^2, and level 4 was S-1 80 mg/m^2/day and gemcitabine 1000 mg/m^2.

The prophylactic administration of granulocyte-colony stimulating factor was not permitted. Administration of granulocyte-colony stimulating factor was permitted in patients with grade 4 neutropenia and/or grade 3 febrile neutropenia. Subsequent courses of chemotherapy were initiated when the leukocyte counts were $4000/mm^3$ or more and platelet counts were $100\,000/mm^3$ or more after day 29. If the leukocyte or platelet counts had not returned to these levels by day 1 of the next course of chemotherapy, both drugs were withheld until full recovery. Treatment was carried out for at least two courses, unless unacceptable toxicity or disease progression occurred.

The planned dose levels are shown in Table 1. At least three patients were enrolled at each dose level. Initially, three patients were treated at dose level 1, and no intrapatient dose escalation was allowed. If one DLT was observed in the first three patients, three more patients were entered at this dose level and dose escalation continued to the next level if fewer than three out of six patients experienced DLT during the first one cycle. The MTD was defined as the previous level from the level at which DLT was observed in two out of three or in three out of six patients during the first one cycle. DLT was defined as (i) grade 3 or greater nonhematological toxicities except nausea/vomiting; (ii) grade 4 thrombocytopenia; (iii) grade 4 neutropenia lasting longer than 4 days; (iv) grade 3 or 4 neutropenia complicated by fever; (v) any unresolved toxicity requiring a delay in the administration of a subsequent course exceeding 8 days;

Table 1 Planned dose of each level

Level	Gemcitabine (mg/m^2)	S-1 (mg/m^2)	Enrolled patients (mg/m^2)	No. of DLT
1	800	60	3	0
2	1000	60	4	0
3	1000	70	6	1
4	1000	80	3	0

DLT, dose-limiting toxicity.

and (vi) any grade 2 toxicity which, in the judgement of the investigator, required dose reduction or discontinuation of therapy. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Second-line chemotherapy or other treatments after this study were not prohibited by the protocol.

Treatment assessment

Patients were evaluated before treatment with a complete blood cell count, a differential count, routine chemistry measurements, a chest radiograph, a chest computed tomographic (CT) scan, an abdominal CT scan, whole-brain magnetic resonance imaging or CT scan, and an isotope bone scan. Evaluations performed weekly were complete blood cell count, differential count, routine chemistry measurements, physical examination, and toxicity assessment. We used the Response Evaluation Criteria in Solid Tumors to assess response to S-1 plus gemcitabine [18]. Responses based on target and nontarget lesions were defined as follows: complete response, disappearance of all target (nontarget) lesions; partial response (PR), or greater 30% reduction in size (or disappearance of one or more nontarget lesions); stable disease, less than 30% decrease and less than 20% increase in size (or the persistence of one or more nontarget lesions); and progressive disease, more than 20% increase in size (or the appearance of new nontarget lesions and/or progression of existing nontarget lesions). The overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence, confirmed by repeated assessments performed no less than 4 weeks after the criteria for response were first met.

Results

Patient characteristics

Between November 2005 and September 2007, 16 patients were enrolled in this study and the clinical characteristics are summarized in Table 2. The number of patients entered at each level is listed in Table 1. The median age of the patients was 76 years (range: 70–86 years). Ten patients were men and six were women. PS, clinical stage, and histology of the patients were as follows: five patients with performance status (PS) 0, 11 patients with PS 1; four patients with stage IIIB, 12 patients with stage IV; and six patients with adenocarcinoma, six patients with squamous cell carcinoma and four patients with nonsmall cell lung cancer. Comorbid disease states were as follows: six patients with chronic obstructive pulmonary diseases; nine patients with hypertension (medically treated); one patient with diabetes mellitus; and three patients with arrhythmia.

Table 2 Patient characteristics

Characteristic	No. of patients
Patients enrolled	16
Age (years)	
Median	76
Range	70–86
Sex	
Male	10
Female	6
PS (ECOG)	
0	5
1	11
Histology	
Adenocarcinoma	6
Squamous cell carcinoma	6
Poor differentiated carcinoma	4
Stage	
IIIB	4
IV	12
Prior treatment	
None	11
Surgery	5

PS (ECOG), performance status (Eastern Cooperative Oncology Group).

Toxicity and treatment cycles

Toxicity was evaluated in all treated patients. The number of patients who developed DLT in the first cycle at each level is listed in Table 1. At level 1, no patients had developed DLT. Three patients developed grade 1–2 diarrhea. The patients, however, improved without intervention. Thus, three patients were started at level 2. At this dose level, no patients had developed DLT, although one patient developed grade 3 neutropenia. Although one patient was added at this dose level, there were no DLTs in four patients. Therefore, three patients were started at level 3. One patient developed grade 3 neutropenia and one patient developed grade 2 hepatotoxicity. One patient developed grade 3 hyperglycemia on day 1, and grade 2 leukopenia and grade 2 neutropenia on day 16. Therefore, three more patients were added at this dose level. One patient developed grade 3 neutropenia and grade 3 leukopenia. One patient developed grade 2 fatigue and grade 2 appetite loss. One patient out of six developed DLT at level 3 and three patients were started at level 4. Two patients developed grade 3 neutropenia and grade 3 leukopenia. At level 4, no patients had developed DLT. We concluded that the MTD was level 4, gemcitabine 1000 mg/m^2 on day 1, 15 and S-1 80 mg/m^2 for 14 consecutive days, followed by a 14-day rest period and the recommended dose for the phase II study was also level 4. The hematological and nonhematological toxicities are listed in Tables 3 and 4.

The median and range of the treatment cycles and the number of patients who received a dose reduction are shown in Table 5. Each patient received 1–6 cycles of therapy, with a median of four cycles.

Response rate

Fourteen patients were assessable for response to treatment (Table 6). A PR was observed in six cases (one of three patients in level 1, one of four patients in level 2, two of six patients in level 3, and two of three patients in level 4). The overall response rate was 42.9%.

Table 3 Hematologic toxicity during first cycle

Level	No. of patients	Leukopenia grade 1/2/3/4	Neutropenia grade 1/2/3/4	Anemia grade 1/2/3/4	Thrombocytopenia grade 1/2/3/4
1	3	0/1/0/0	0/1/0/0	1/0/0/0	0/0/0/0
2	4	1/1/0/0	0/1/3/0	1/0/0/0	0/0/0/0
3	6	0/1/1/0	0/1/2/0	1/0/0/0	1/0/0/0
4	3	0/1/2/0	0/1/2/0	0/0/0/0	0/0/0/0

Table 4 Nonhematologic toxicity during first cycle

Level	No. of patients	Diarrhea grade 1/2/3/4	Fever grade 1/2/3/4	Appetite loss grade 1/2/3/4	Nausea/vomitting grade 1/2/3/4	Liver grade 1/2/3/4	Fatigue grade 1/2/3/4	Rash grade 1/2/3/4	Hyperglycemia grade 1/2/3/4
1	3	2/1/0/0	2/0/0/0	1/1/0/0	1/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0
2	4	0/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0	0/0/0/0
3	6	0/0/0/0	2/0/0/0	2/1/0/0	3/0/0/0	0/2/0/0	0/1/0/0	0/0/0/0	0/0/1/0
4	3	0/0/0/0	0/0/0/0	1/0/0/0	1/0/0/0	0/0/0/0	0/0/0/0	0/1/0/0	0/0/0/0

Table 5 Duration of administration and dose intensity

Level	Gemcitabine/ S-1 (mg/m^2)	No. of patients	No. of cycles		Cycles with dose reduction in gemcitabine	
			Total	Median (range)	Number	%
1	800/60	3	12	4 (2–6)	0	0
2	1000/60	4	19	4 (3–6)	0	0
3	1000/70	6	22	4 (1–6)	3	13.6
4	1000/80	3	13	4 (3–6)	0	0

Table 6 Response rate

Tumor response	No. of patients (level 1/2/3/4)
Complete	0 (0/0/0/0)
Partial	6 (1/1/2/2)
Stable disease	8 (1/2/4/1)
Progressive disease	0 (0/0/0/0)
Not evaluable	2 (1/1/0/0)
Overall response rate (%)	42.9

Discussion

This is the first report of a phase I study designed to determine the DLT and MTD of S-1 plus gemcitabine for the treatment of chemotherapy-naive elderly patients with advanced NSCLC. The MTD and recommended dose of the combination were defined at dose level 4, that is, S-1 80 mg/m^2 and gemcitabine 1000 mg/m^2. All enrolled patients (16) were evaluated for toxicity. Six PRs, with an overall response rate of 42.9% were noted. Hematological toxicities were mild in our study. Grade 3 neutropenia occurred in 43.7% of patients; three of four patients in level 2, two of six patients in level 3, and two of three patients in level 4. No febrile neutropenia was detected. No patients experienced grade 3 or 4 thrombocytopenia. Nonhematologic toxicities were also mild. Although grade 3 hyperglycemia was observed in one patient, the patient improved without intervention. No other patient experienced grade 3 or 4 nonhematological toxicities. No patients experienced hematological toxicity requiring a delay in the administration of a subsequent course exceeding 8 days.

Recently, prospective trials that specifically address the role of chemotherapy in elderly individuals with NSCLC have been designed and conducted. A randomized phase III trial [Elderly Lung Cancer Vinorelbine Italian Study (ELVIS)] has demonstrated that vinorelbine monotherapy improves quality of life and survival in advanced NSCLC patients aged 70 years or older compared with supportive care alone, thus establishing the potential of chemotherapy in this age group [19]. Gemcitabine has demonstrated promising activity with good tolerability in a number of retrospective analysis in which no differences were noted between elderly and younger patients with respect to response or survival [2,20]. The Multicenter Italian Lung Cancer in the Elderly Study (MILES) trial demonstrated that single-agent therapy with vinorelbine or gemcitabine is preferable to the combination for treatment of advanced NSCLC in elderly patients [21]. Although several retrospective subset analyses of platinum-based chemotherapy trials have demonstrated no or minimal differences between elderly and younger patients, no elderly specific prospective phase III trials of platinum-based therapy in NSCLC have been conducted previously [2,22]. At present, single-agent chemotherapy of vinorelbine or gemcitabine seems to be a reasonable choice on elderly patients with advanced NSCLC.

S-1 is a novel anticancer drug, and the efficacy and survival rate of combination chemotherapy with S-1 and cisplatin are reported to be favorable in advanced NSCLC [10]. This drug also has minimal adverse effects and is presumed to be well tolerated in elderly patients. In this study with S-1, the treatment modality was determined based on the phase I/II trial of S-1 plus gemcitabine in patients with metastatic pancreatic cancer [15–17]. Nakamura *et al.* [15] showed that the recommended dose is gemcitabine 1000 mg/m^2 on day 8, 15 and S-1 60 mg/m^2 for 14 consecutive days, followed by a 7-day rest period. Ueno *et al.* [17] also described that the recommended dose is gemcitabine 1000 mg/m^2 on day 1, 8 and S-1 80 mg/m^2 for 14 consecutive days, followed by a 7-day rest period. Biweekly administration of gemcitabine is shown

to be active without increasing toxicity in patients with advanced NSCLC [23]. The biweekly administration of 5-FU and gemcitabine is also shown to be well tolerated and promising for the treatment of advanced colorectal cancer [24]. Biweekly administration of anticancer agents was described to be feasible and effective in elderly patients with advanced NSCLC [25,26]. Considering the treatment in elderly patients with NSCLC, we planned that S-1 would be administered for 14 days followed by a 14-day rest and the schedule was repeated every 4 weeks other than 3 weeks for use in an outpatient treatment setting. Biweekly administration of gemcitabine also contributes to biweekly hospital visits during this outpatient treatment. Although efficacy was not a primary endpoint of this study, 42.9% of our patients achieved a PR and seemed to be similar to the results of the platinum-based chemotherapy [27,28].

The first course of chemotherapy was conducted by hospitalization for all patients, but the second or subsequent courses could be performed at an outpatient clinic for all of 16 patients. Moreover, oral administration of S-1, which eliminates the cost and inconveniences of infusion pumps and catheters with their potential risks of infection and thrombosis, also contributes to fewer hospital visits during this outpatient treatment. Anticancer treatment for advanced NSCLC would be preferable on an outpatient rather than an inpatient basis, given the short life expectancy and quality of life considerations. In treatment for patients with advanced NSCLC, it is important to not only improve the prognosis of advanced NSCLC but also create a feasible regimen of chemotherapy that does not require hospitalization. These results indicated that the combination at the recommended dose selected in this study is quite feasible in outpatient treatment setting.

In conclusion, the results of this study indicate that the combination of S-1 plus gemcitabine is a safe and well-tolerated regimen in elderly patients with advanced NSCLC. The optimal dosage schedule for a phase II study is gemcitabine 1000 mg/m^2 on day 1, 15 and S-1 80 mg/m^2 for 14 consecutive days, followed by a 14-day rest period. A multicenter phase II trial is already ongoing to further evaluate the efficacy and the toxicity of this regimen.

Acknowledgements

The authors thank Satoshi Tsuchiya of Tsuchiya Clinic for assistance in the design of this study.

References

1 Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer. A meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995; **311**:899–909.
2 Gridelli C, Shepherd FA. Chemotherapy for elderly patients with non-small cell lung cancer: a review of the evidence. *Chest* 2005; **128**:947–957.
3 Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; **341**:2061–2067.
4 Yee KW, Pater JL, Pho L, Zee B, Siu LL. Enrollment of older patients in cancer treatment trials in Canada: why is age a barrier? *J Clin Oncol* 2003; **21**:1618–1623.
5 Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, *et al*. 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. *Anticancer Drugs* 1996; **7**:548–557.
6 Tatsumi K, Fukushima M, Shirasaka T, Fujii S. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res* 1987; **78**:748–755.
7 Takechi T, Fujioka A, Matsushima E, Fukushima M. Enhancement of the antitumour activity of 5-fluorouracil (5-FU) by inhibiting dihydropyrimidine dehydrogenase activity (DPD) using 5-chloro-2,4-dihydroxypyridine (CDHP) in human tumour cells. *Eur J Cancer* 2002; **38**:1271–1277.
8 Takechi T, Nakano K, Uchida J, Mita A, Toko K, Takada S, *et al*. Antitumour activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother Pharmacol* 1997; **39**:205–211.
9 Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S, *et al*. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 2001; **85**:939–943.
10 Ichinose Y, Yoshimori K, Sakai H, Nakai Y, Sugiura T, Kawahara M, *et al*. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004; **10**:7860–7864.
11 Kaira K, Sunaga N, Yanagitani N, Imai H, Utsugi M, Shimizu Y, *et al*. A phase I dose escalation study of S-1 plus carboplatin in patients with advanced non-small cell lung cancer. *Anticancer Drugs* 2007; **18**:471–476.
12 Hertel LW, Kroin JS, Misner JW, Tustin JM. Synthesis of 2-deoxy-2,2-difluro-D-ribose and 2-deoxy-2,2-D-ribofuranosyl nucleosides. *J Org Chem* 1988; **53**:2406–2409.
13 Seto T, Yoh K, Asoh H, Yamamoto H, Semba H, Ichinose Y. A phase I study of combination chemotherapy with gemcitabine and oral UFT for advanced non-small cell lung cancer. *Br J Cancer* 2002; **86**:1701–1704.
14 Ichinose Y, Seto T, Semba H, Itoh K, Inoue Y, Tanaka F, *et al*. UFT plus gemcitabine combination chemotherapy in patients with advanced non-small-cell lung cancer: a multi-institutional phase II trial. *Br J Cancer* 2005; **93**:770–773.
15 Nakamura K, Yamaguchi T, Ishihara T, Kobayashi A, Tadenuma H, Sudo K, *et al*. Phase I trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. *Br J Cancer* 2005; **92**:2134–2139.
16 Nakamura K, Yamaguchi T, Ishihara T, Sudo K, Kato H, Saisho H. Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. *Br J Cancer* 2006; **94**:1575–1579.
17 Ueno H, Okusaka T, Ikeda M, Ishiguro Y, Morizane C, Matsubara J, *et al*. A phase I study of combination chemotherapy with gemcitabine and oral S-1 for advanced pancreatic cancer. *Oncology* 2005; **69**:421–427.
18 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al*. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92**:205–216.
19 Elderly Lung Cancer Vinorelbine Italian Study. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. *J Natl Cancer Inst* 1999; **91**:66–72.
20 Shepherd FA, Abratt RP, Anderson H, Gatzemeier U, Anglin G, Iglesias J, *et al*. Gemcitabine in the treatment of elderly patients with advanced non-small cell lung cancer. *Semin Oncol* 1997; **24** (**Suppl**):S50–S55.
21 Gridelli C, Perrone F, Gallo C, Cigolari S, Rossi A, Piantedosi F, *et al*. Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003; **95**:362–372.
22 Langer CJ, Manola J, Bernardo P, Kugler JW, Bonomi P, Cella D, *et al*. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst* 2002; **94**:173–181.
23 Lopez-Vivanco G, Viteri A, Barcelo R, Munoz A, Rubio I, Mane JM, *et al*. Biweekly administration of cisplatin/gemcitabine in advanced non-small cell lung cancer. *Am J Clin Oncol* 2005; **28**:501–507.
24 Correale P, Messinese S, Caraglia M, Marsili S, Piccolomini A, Petrioli R, *et al*. A novel biweekly multidrug regimen of gemcitabine, oxaliplatin,

5-fluorouracil (5-FU), and folinic acid (FA) in pretreated patients with advanced colorectal carcinoma. *Br J Cancer* 2004; **90**:1710–1714.
25 Yanagitani N, Tsuchiya S, Kaira K, Sunaga N, Tsuchiya Y, Sato K, *et al*. Phase I study of biweekly paclitaxel and carboplatin for frail patients with advanced non-small cell lung cancer. *Am J Clin Oncol* 2007; **30**: 487–491.
26 Tomizawa Y, Ishihara S, Iijima H, Imai H, Sato K, Yatomi M, *et al*. A phase I dose escalation study of biweekly gemcitabine and carboplatin in completely resected stage IB–IIIA nonsmall cell lung cancer. *Am J Clin Oncol* 2007; **30**:498–502.
27 Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, *et al*. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 2002; **346**:92–98.
28 Kaira K, Takise A, Minato K, Iwasaki Y, Ishihara S, Takei Y, *et al*. Phase II study of weekly docetaxel and cisplatin in patients with non-small cell lung cancer. *Anticancer Drugs* 2005; **16**:455–460.