Patients and Methods

Patients. This study was undertaken at the Department of Medical Oncology, Kinki University Faculty of Medicine, and patients with lung adenocarcinoma who received TRT were eligible for inclusion. Individuals with stage I, recurrent, or metastatic disease and those treated with stereotactic radiotherapy were excluded. From February 2003 to October 2010, 130 patients with unresectable locally advanced NSCLC were treated with TRT-alone or together with chemotherapy. Histo-pathological results for 48 patients were consistent with a diagnosis of lung adenocarcinoma. The present study included 37 of these adenocarcinoma patients for whom tumor specimens were available.

Data were collected by a retrospective scan and a chart review for each patient and included age, sex, Eastern Cooperative Oncology Group performance status, smoking history, chemotherapy regimen with radiotherapy, efficacy data (PFS, overall survival (OS), and response), and type of recurrence after TRT. Smoking status was classified as never-smokers (<100 cigarettes in a lifetime), former, or current smokers. Local recurrence was defined as the detection of a tumor within the same lung or in the ipsilateral mediastinal, hilar, or supraclavicular lymph node; distant recurrence was defined as any other type of recurrence. Two investigators (H.H. and I.O.) assessed computed-tomographic or computed-tomographic positron-emission tomographic images if the type of recurrence was not recorded by the attending physician. The initial tumor response was defined as the best response recorded within three months after the start of TRT, as assessed according to RECIST version 1.1 (14). PFS was calculated from the start of TRT until the first documented instance of disease progression or death, and OS was defined as the time from diagnosis to death. We also assessed the frequency of treatment with EGFR-TKIs subsequent to recurrence after TRT for patients harboring *EGFR* mutations and considered its impact on survival time.

Analysis of EGFR mutations and EML4–ALK rearrangement. To detect *EGFR* mutations and the *EML4–ALK* rearrangement, we obtained formalin-fixed, paraffin-embedded NSCLC tissue specimens from the patients from the archives of Kinki University Faculty of Medicine. *EGFR* mutations were identified with a polymerase chain reaction-based allele-specific screening for common exon 19 deletions and missense mutations in exons 18 and 21 (15, 16). The presence of *EML4–ALK* was detected with the use of the MassARRAY method (Sequenom, San Diego, CA, USA). The sequences of PCR primers and assay conditions are available on request. The variant of *EML4–ALK* was confirmed by cloning the PCR products into a TA cloning vector (Invitrogen, Madison, WI, USA).

Statistical analysis. Descriptive analyses were performed on three molecularly defined groups: *EML4–AL-* positive, *EGFR* mutation-positive, and double-negative. Associations between such molecular status and clinical data were examined with the chi-square or Fisher's exact test. Survival (OS and PFS) analysis was performed by the Kaplan–Meier method, and curves were compared with the log-rank test. All statistical tests were two-sided and were performed with the SPSS version 14.0 software (SPSS, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Table I. *Patients' characteristics according to epidermal growth factor receptor gene (EGFR) mutations and echinoderm microtubule-associated protein-like 4 (EML4)– anaplastic lymphoma kinase (ALK) rearrangement status.*

	All patients	*EGFR* mutation-positive (n=11)	*EML4–ALK* positive (n=3)	Double-negative (n=23)
Gender				
Male	29	6	3	20
Female	8	5	0	3
Median age (years)	67	74	71	64
Smoking status				
Never-smoker	12	7	0	5
Current/former smoker	25	4	3	18
ECOG PS				
0/1	36	11	3	22
2	1	0	0	1
Stage				
IIB	1	1	0	0
IIIA	19	5	2	12
IIIB	17	5	1	11
Chemotherapy with TRT				
Platinum based	26	6	1	19
Nonplatinum based	6	4	1	1
None	5	1	1	3

ECOG PS: Eastern Cooperative Oncology Group performance status; TRT: thoracic radiotherapy.

Results

Patients' characteristics. Table I shows the characteristics of the 37 patients with locally advanced lung adenocarcinoma treated with TRT. Eleven (29.7%) patients had tumors positive for an *EGFR* mutations, 3 (8.1%) had tumors manifesting *EML4–ALK* rearrangement, and 23 (62.2%) had tumors negative for both types of molecular changes. Tumors positive for both *EGFR* mutation and the *EML4–ALK* rearrangement were not observed. *EGFR* mutations in exons 18, 19, and 21 were detected in two (5.4%), four (10.8%), and five (13.5%) patients, respectively. *EGFR* mutations were present preferentially in women and never-smokers (p=0.035 and 0.018, respectively, Fisher's exact test).

Efficacy of TRT with or without chemotherapy according to the molecular subtype of adenocarcinoma. We examined the potential impact of *EGFR* mutations and *EML4–ALK* rearrangement on survival. At the time of analysis, 31 patients had experienced disease progression and 25 patients had died. The median follow-up time was 20.7 months for all patients. Median PFS and OS for all patients were 11.6 months [95% confidence interval (CI)=5.1 to 18.1] and 42.6 months (95% CI=12.3 to 72.8), respectively (Table II). A

Table II. *Outcome of thoracic radiotherapy (TRT) based on epidermal growth factor receptor gene (EGFR) mutations and echinoderm microtubule-associated protein-like 4 (EML4)– anaplastic lymphoma kinase (ALK) rearrangement status.*

	All patients	*EGFR* mutation-positive (n=11)	*EML4–ALK*-positive (n=3)	Double-negative (n=23)
Response rate (%)	73.0	90.9	66.7	65.2
Median PFS (95% CI)	11.6 months (5.1-18.1)	13.1 months (6.9-19.4)	4.2 months* (3.5-5.0)	18.6 months (2.6-34.6)
Median OS (95% CI)	42.6 months (12.3-72.8)	67.5 months (15.4-122.7)	7.7 months† (4.6-10.7)	42.6 months (27.6-57.6)
Type of first recurrence				
Local recurrence	8	5‡	0	3
Distant metastasis	22	3	3	16
None	7	3	0	4

PFS: Progression-free survival; OS: overall survival; CI: confidence interval. *p=0.037 (log-rank test), †p=0.007 (log-rank test), ‡p=0.052 (Fisher's exact test) *versus* double-negative.

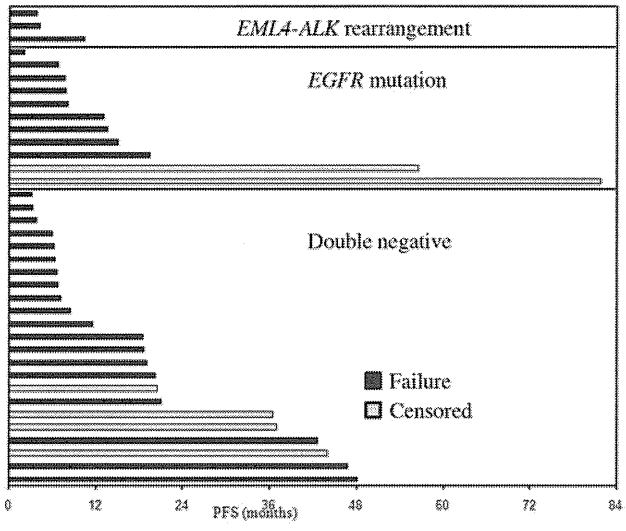

Figure 1. *Waterfall plot of progression-free survival (PFS) for patients with epidermal growth factor receptor gene (EGFR) mutations, echinoderm microtubule-associated protein-like 4 (EML4) – anaplastic lymphoma kinase (ALK) rearrangement, or neither molecular change. Patients still receiving treatment were censored for progression at the time of analysis.*

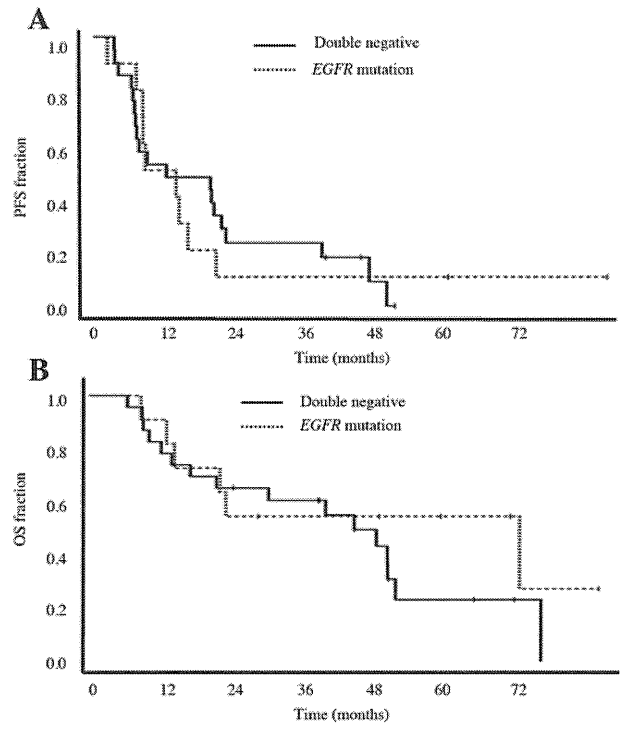

Figure 2. *Kaplan–Meier plots of progression-free survival (PFS) (A) and overall survival (OS) (B) for patients with epidermal growth factor receptor gene (EGFR) mutation-positive or double-negative disease.*

waterfall plot of PFS and Kaplan-Meier curves for PFS and OS for patients, according to the molecular subgroup are shown in Figures 1 and 2, respectively. The median PFS and OS were 13.1 and 69.0 months, respectively, for patients with *EGFR* mutations, 4.2 and 7.7 months for those with *EML4–ALK*, and 18.6 and 42.6 months for those negative for both molecular changes (Table II). Although there was no significant difference in PFS or OS between patients with *EGFR* mutation-positive tumors and those who were double-negative, the PFS and OS of patients with the *EML4–ALK* rearrangement were significantly reduced compared to those with double-negative tumors. With respect to the type of recurrence, the rate of local recurrence for patients with *EGFR* mutation-positive disease was higher than that for those with double-negative (45.5 *versus* 13.0%, respectively, p=0.052).

Discussion

As far as we are aware, our study is the first to determine the proportion of Asian patients with locally advanced lung cancer who harbor *EGFR* mutations or the *EML4–ALK* fusion gene. Our analysis revealed that the prevalence of *EGFR* mutations (29.7%) and of the *EML4–ALK* rearrangement (8.1%), in cases of locally advanced lung adenocarcinoma, is similar to the one previously determined for cases of metastatic disease, and that *EGFR* mutations among patients with locally advanced adenocarcinoma occur preferentially in women and never-smokers, again as happens in cases of metastatic disease (17).

We also examined the effect of TRT on OS and PFS in patients classified according to the molecular subtype of locally advanced adenocarcinoma of the lung. The PFS of patients with *EGFR* mutations was similar to that of those with double-negative disease. Despite the small number of patients, this result is consistent with those of previous studies on larger numbers of Caucasian patients with locally advanced NSCLC showing equivalent relapse-free survival rates for individuals with and without *EGFR* mutations (18). Our analysis also revealed a tendency of higher incidence of local recurrence for *EGFR* mutation-positive NSCLC than for double-negative NSCLC, suggesting that the effect of radiation at local sites was insufficient in the former group of patients. Pre-clinical studies have shown that NSCLC cells harboring *EGFR* mutations have a predominantly radiosensitive phenotype associated with a delay in the repair of radiation-induced DNA damage, defective radiation-induced arrest of DNA synthesis or mitosis, and a pronounced increase in the frequency of radiation-induced apoptosis (19). However, our results now suggest that such preclinical findings showing the radiation sensitivity of NSCLC cells harboring *EGFR* mutations might not be applicable to the clinical setting. The OS of patients with *EGFR* mutation-positive disease was substantially longer than that of patients with double-negative disease in the present study, although this difference was not statistically significant. Of note, 6 out of the 11 patients with *EGFR* mutations underwent EGFR-TKI treatment subsequent to relapse after TRT. Long-term disease stabilization or tumor shrinkage in response to EGFR-TKI treatment has been demonstrated in *EGFR* mutation-positive metastatic NSCLC. Treatment with EGFR-TKIs subsequent to disease recurrence after TRT may therefore also increase OS of patients with locally advanced disease.

Several prospective trials of EGFR-TKI treatment have revealed a marked improvement in clinical outcome for patients with advanced NSCLC positive for *EGFR* mutations and have validated the selection of patients based on molecular status (9-12). Evaluation of *EGFR* mutation status for patients with metastatic NSCLC is now recognized as mandatory for proper selection of therapy. Our results now suggest that such a molecular basis for therapy selection may also be warranted for patients with locally advanced NSCLC, for whom targeted therapies have yet to be established. We previously examined the feasibility of treatment with the EGFR-TKI gefitinib in combination with concurrent TRT in patients with locally advanced *EGFR* mutation-positive NSCLC (20). In the previous study, two patients with *EGFR* mutations (deletions in exon 19) did not experience local progression and exhibited an OS of >5 years. Given the presence of *EGFR* mutations in a substantial proportion of patients with NSCLC, even those with locally advanced disease, further trials of targeted agents, including EGFR-TKIs, in combined-modality regimens are warranted for molecularly selected populations.

We also detected EML4–ALK rearrangement in a sizeable proportion (8.1%) of nonselected patients with locally advanced lung adenocarcinoma. These patients had a poor outcome after TRT. As far as we are aware, the relation between radiosensitivity and *EML4–ALK* rearrangement has not been previously examined even in the pre-clinical setting. Preclinical and clinical evaluation of the radiosensitivity of NSCLC positive for *EML4–ALK* is thus needed.

In conclusion, we have found that a substantial proportion of patients with locally advanced adenocarcinoma of the lung harbor *EGFR* mutations or a *EML4–ALK* rearrangement. The efficacy of TRT was limited for patients with *EGFR* mutations, and those with the *EML4–ALK* fusion gene had an even poorer outcome after such treatment. Our data thus provide a basis for future studies of such molecularly selected patients with locally advanced NSCLC.

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PHASE I STUDIES

A phase I study of S-1 with concurrent radiotherapy in elderly patients with locally advanced non-small cell lung cancer

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Summary *Background* A phase I study was performed to evaluate dose-limiting toxicity and the recommended dose for the oral fluoropyrimidine S-1 administered concurrently with thoracic radiotherapy (TRT) in elderly (≥70 years of age) patients with locally advanced non-small cell lung cancer. *Methods* S-1 was administered on days 1 to 14 and 22 to 35 at oral doses of 65 or 80 mg m^{-2} day^{-1}. TRT was administered in 2-Gy fractions five times weekly for a total dose of 60 Gy. Twelve previously untreated patients were treated with S-1 at 65 (n=6) or 80 (n=6) mg m^{-2} day^{-1}. *Results* All patients completed the planned 60 Gy of TRT. Dose-limiting toxicity included pneumonitis (n=2), infection (n=1), and stomatitis (n=1), each of grade 3, but each event was reversible. The recommended dose for S-1 was determined to be 80 mg m^{-2} day^{-1}. No patient experienced toxicity of grade 4. The dose intensity of S-1 was well maintained and the combination of S-1 plus TRT was well tolerated overall. The overall response rate was 83.3 %, with a median survival time of 34.0 months. *Conclusions* Administration of S-1 at 80 mg m^{-2} day^{-1} on days 1 to 14 and 22 to 35 can be safely combined with concurrent TRT in elderly patients with locally advanced non-small cell lung cancer.

Keywords Locally advanced · Non-small cell lung cancer · Elderly · Chemoradiation · S-1

Introduction

The incidence of lung cancer, the leading cause of cancer-related deaths, increases with age. As a result of the recent substantial increase in life expectancy in the general population, non-small cell lung cancer (NSCLC) is now a relatively common disease among the elderly. The question of how best to treat older individuals with NSCLC has thus become increasingly important.

NSCLC accounts for 80 % of all lung cancer cases, and ~30 % of patients with NSCLC present with locally advanced disease. Individuals with locally advanced NSCLC have a chance of long-term disease-free survival and may possibly be cured by instigation of appropriate combined-modality therapies. The treatment goal for locally advanced NSCLC thus differs from that for incurable metastatic NSCLC. The results of phase III

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studies have led to the adoption of platinum-based chemotherapy with concurrent thoracic radiotherapy (TRT) as the standard treatment for locally advanced NSCLC of stage III [1]. However, elderly patients are underrepresented in such clinical trials, with even those with a good performance status often being considered unfit for aggressive combined chemoradiotherapy on the basis of the assumptions that the risk of severe toxicity is exacerbated by age and that the benefits of such treatment for such individuals are limited in terms of prognosis [2–4]. The development of new potent agents suitable for combination with TRT in the elderly population is thus needed.

S-1 is an oral anticancer agent comprising tegafur, 5-chloro-2,4-dihydroxypyridine (gimeracil), and potassium oxonate in a molar ratio of 1:0.4:1 [5]. Tegafur, a prodrug of 5-fluorouracil (5-FU), is gradually converted to 5-FU, which is rapidly catabolized by dihydropyrimidine dehydrogenase in the liver. 5-Chloro-2,4-dihydroxypyridine is a competitive inhibitor of 5-FU catabolism, and potassium oxonate limits the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase. A phase II trial of oral S-1 as a single agent for the treatment of advanced NSCLC yielded a response rate of 22 % and a median survival time of 10.2 months and was associated with mild toxicities in 59 patients without prior chemotherapy [6]. Preclinical models have revealed that S-1 enhances the antitumor activity of radiation [7, 8]. Indeed, we and others have recently shown that S-1 and cisplatin chemotherapy with concurrent TRT has promising activity with acceptable toxicities in patients with locally advanced NSCLC (20 to 74 years of age) [9, 10]. indicating that S-1 with concurrent TRT may be of therapeutic benefit. We have now performed a phase I study to evaluate dose-limiting toxicity (DLT) and the recommended dose (RD) for S-1 administered concurrently with TRT in elderly (≥70 years of age) patients with locally advanced NSCLC.

Patients and methods

Patients

Eligible patients were required to have histologically or cytologically proven unresectable NSCLC of stage IIIA or IIIB. Other eligibility criteria included no previous chemotherapy or radiotherapy; a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale; an age of ≥70 years; a life expectancy of at least 12 weeks; adequate bone marrow reserve (leukocyte count of ≥4000/mm^3, neutrophil count of ≥2000/mm^3, platelet count of ≥100,000/mm^3, and hemoglobin concentration of ≥9 g/dL); normal liver function (total serum bilirubin of ≤1.5 mg/dL as well as aspartate transaminase and alanine transaminase levels of less than twice the upper limit of the normal range); a 24-h creatinine clearance of ≥60 mL/min; and a partial pressure of arterial oxygen of ≥70 torr. Patients were excluded if they had an active additional malignancy; a concomitant serious illness such as uncontrolled angina pectoris; a myocardial infarction in the previous 3 months; heart failure; uncontrolled diabetes mellitus; uncontrolled hypertension; interstitial pneumonia or lung disease; or an infection or other condition contraindicating chemotherapy or radiotherapy. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Treatment

Patients received an oral dose of S-1 twice daily after meals on days 1 to 14 and 22 to 35 (Fig. 1). Given that S-1 is available for use only in capsules of 20 or 25 mg, the individual daily dose was set as 50 mg/day for a body surface area (BSA) of <1.25 m^2, 80 mg/day for 1.25 m^2≤BSA<1.5 m^2, or 100 mg/day for a BSA of ≥1.5 m^2 at the dose level of 65 mg m^{-2} day^{-1}, or 80 mg/day for a BSA of <1.25 m^2, 100 mg/day for 1.25 m^2≤BSA<1.5 m^2, or 120 mg/day for a BSA of ≥1.5 m^2 at the dose level of 80 mg m^{-2} day^{-1}. The subsequent cycle of chemotherapy was delayed if any of the following toxicities were noted on day 1: leukocyte count of <2000/mm^3, neutrophil count of <1000/mm^3, platelet count of <75,000/mm^3, serum creatinine level of ≥1.5 mg/dL, fever of ≥38°C, or nonhematologic toxicity of grade 3 or 4.

All patients were treated with a linear accelerator photon beam of at least 10 MV. The primary tumor and involved nodal disease received 60 Gy in 2-Gy daily fractions for five consecutive days each week over 6 weeks. Radiation doses were specified at the center of the target volume. Doses were calculated based on the assumption of tissue homogeneity without correction for lung tissue. The initial 40 Gy was delivered to clinical target volume (CTV) 1, and the final 20 Gy was delivered to a reduced volume designated CTV2. CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to subcarinal lymph nodes, but not the contralateral hilum. For the primary tumor and involved lymph nodes, a margin of 1.5 to 2 cm was added. CTV2 included only the primary tumor and involved lymph nodes, with a margin of 0.5 to 1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods, such as the oblique opposing method. Appropriate planning target volume margin and leaf margin were added for CTV1 and CTV2. TRT was suspended if any of the following toxicities were noted: leukocyte count of <1000/mm^3, neutrophil count of <500/mm^3, platelet count of <25,000/mm^3, fever

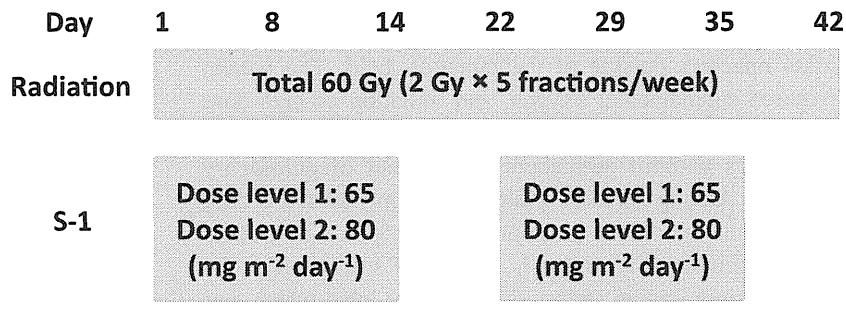

Fig. 1 Treatment scheme and dose escalation

of ≥38°C, esophagitis or dermatitis of grade 3 or 4, a partial pressure of arterial oxygen of <60 torr, or suspected radiation pneumonitis. If a hematologic toxicity of grade 3 or 4 occurred, TRT was withheld until recovery to grade 2.

Definition of maximum tolerated dose (MTD), RD, and DLT

The MTD was defined as the dose level at which DLT occurs in >50 % of patients treated, with the preceding dose level then being the RD. Three patients were initially enrolled at dose level 1. If one or two patients experienced DLT, three additional patients were treated at the same dose level. If no more than three of the six patients experienced DLT, the next cohort of patients was treated at dose level 2. If none to two of the initial three patients experienced DLT at dose level 2, an additional three patients were treated at this dose level. If fewer than three of the six patients experienced DLT, dose level 2 was defined as the RD. Dose escalation to a level higher than level 2 (80 mg m^{-2} day^{-1}) was not allowed because this level is the MTD for daily monotherapy. DLT was defined as: (1) neutropenia of grade 4 persisting for 4 days or longer, (2) febrile neutropenia, (3) a platelet count of <20,000/mm^3, (4) nonhematologic toxicity of grade 3 or 4 other than appetite loss, nausea, or vomiting, (5) inability to take the scheduled oral dose of S-1 for more than 3 out of 4 weeks, (6) inability to receive the scheduled 60 Gy of TRT within 8 weeks, or (7) inability to receive TRT of >50 Gy because of adverse events.

Safety and efficacy assessment

Complete blood cell counts and serum chemistry profile were determined and a physical examination and chest x-ray were performed at least once a week during treatment. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [11]. Survival time was defined as the interval between the date of treatment initiation and the date either of death due to any cause or of the most recent follow-up evaluation. Survival curves were estimated by the Kaplan-Meier method. All statistical analyses were performed with SPSS 16.0 for Windows software (SPSS, Chicago, IL).

Results

Patients

Sixteen patients (13 men, 3 women) were enrolled in the trial. Four of these individuals were subsequently found to be ineligible; the performance status of two patients worsened before the start of the treatment, one patient developed dementia after hospitalization, and one patient was found to have distant metastasis. Twelve patients were thus eligible (six for dose level 1 and six for dose level 2). Patient characteristics are summarized in Table 1. The 10 men and 2 women had a median age of 77 years (range, 73 to 82). Half of the patients had squamous cell carcinoma, and half had a performance status of 1. Seven patients were in stage IIIA of the disease, and five were in stage IIIB.

Dose escalation and DLT

Among the first three patients treated at dose level 1, one individual developed DLT, pneumonitis of grade 3 that was considered radiation toxicity. The patient had completed the protocol treatment without interruption. Acutely deteriorating dyspnea with fever and cough was apparent 19 days after the end of the treatment. A chest computed

Table 1 Patient characteristics

No. of patients	12
Median age, years (range)	77 (73–82)
Sex: male/female	10/2
Performance status: 0/1	6/6
Histology	
Adenocarcinoma	5
Squamous cell carcinoma	6
Unclassified	1
Smoking: ever/never	9/3
Stage of disease: IIIA/IIIB	7/5

tomography (CT) scan revealed extensive bilateral ground-glass opacities outside of the radiation field. The patient required supplemental oxygen, and initiation of high-dose methylprednisolone treatment resulted in amelioration of his symptoms without permanent impairment of pulmonary function. Among the three additional patients treated at dose level 1, one individual developed DLT, infection of grade 3 without neutropenia, on day 9. A chest CT scan revealed the central tumor and an atelectatic left upper lobe, which was considered to reflect obstructive pneumonia. The administration of S-1 was stopped immediately, and the patient improved after antibiotic treatment. Two of the six patients treated at dose level 1 thus developed DLT.

At dose level 2, none of the first three patients developed DLT. According to the study protocol, an additional three patients were enrolled, two of whom developed DLT. One patient developed stomatitis of grade 3 that required postponement of S-1 administration, which was resumed at the lower dose level after 8 days. The second patient experienced pneumonitis of grade 3 associated with radiation toxicity at 258 days after the end of the protocol treatment, which had been completed without interruption; supplemental oxygen was required, and symptoms rapidly resolved after the start of high-dose steroid treatment, without permanent impairment of pulmonary function. The MTD was thus not reached, and dose level 2 was determined to be the RD.

Other non-DLT toxicities

Hematologic and nonhematologic toxicities are summarized in Table 2. There were no toxicities of grade 4. The most frequent adverse effects were pneumonitis (7 patients including 2 DLTs), leukopenia (7 patients), anemia (5 patients), and esophagitis (5 patients). Most of these events were of mild-to-moderate intensity and of CTCAE grade 1 or 2.

Table 2 Toxicities

S-1 dose level		1			2	
No. of patients enrolled		6			6	
Toxicity grade	Any	3	4	Any	3	4
Leukopenia	4	0	0	3	2	0
Neutropenia	1	1	0	2	1	0
Anemia	3	0	0	2	0	0
Thrombocytopenia	1	0	0	2	0	0
Stomatitis	1	0	0	3	1[a]	0
Esophagitis	4	0	0	1	0	0
Infection	3	1[a]	0	1	0	0
Pneumonitis	4	1[a]	0	3	1[a]	0
Diarrhea	1	0	0	1	0	0
Dermatitis	1	0	0	1	0	0

[a] Dose-limiting toxicity

Treatment delivery

All 12 patients completed the planned TRT within 8 weeks. The planned two cycles of S-1 and TRT were administered in 87.5 and 95.0 % of patients, respectively, at S-1 dose level 1 and in 98.4 and 99.0 % of patients, respectively, at dose level 2 (Table 3). Interruption or delay of S-1 administration was instituted in three patients. Two of these patients developed DLT, stomatitis of grade 3 at dose level 1 and infection of grade 3 at dose level 2. In another patient treated at dose level 1, the protocol treatment was postponed for 8 days because of bronchial infection of grade 2 without neutropenia.

Objective response and survival

All patients were evaluable for response. A partial response was observed in 10 of the 12 patients, stable disease in 1 patient, and progressive disease in 1 patient. The median follow-up time was 9.5 months (range, 1.6 to 52.3), and the overall response rate was 83.3 % (95 % confidence interval, 58.6 to 100.0). Median progression-free survival time and median survival time were 18.2 and 34.0 months, respectively. The primary tumor inside the radiation field was the site of initial failure in three patients, whereas distant metastasis was the cause of failure in four patients. There was no evidence of recurrent disease in five patients.

Discussion

We have performed a phase I study of S-1 with concurrent TRT for elderly patients with locally advanced NSCLC. The RD and schedule for S-1 were determined to be 80 mg m^{-2} day^{-1} on days 1 to 14 and 22 to 35, administered

Table 3 Dose intensity

S-1 dose level	1	2
No. of patients	6	6
S-1 (%)[a]	87.5	98.4
TRT (%)[b]	95.0	99.0
Total radiation dose (Gy)		
60	6	6
50–59	0	0
Radiotherapy delay (days)		
0	5	5
1–7	0	1
8–14	1	0

[a] Administered drug dose (mg m^{-2} $week^{-1}$)/projected dose (mg m^{-2} $week^{-1}$)

[b] Actual RT dose (Gy/week)/projected TRT dose (Gy/week)

with TRT at a total dose of 60 Gy in daily fractions of 2 Gy. Toxicities were generally well tolerated. The principal non-hematologic toxicities were esophagitis, stomatitis, and pneumonitis. Esophagitis was readily monitored and manageable with standard supportive treatment. Severe stomatitis was considered a DLT in one patient, but this adverse event was an out-of-field complication and was also found to occur at a low frequency in a previous study of S-1 monotherapy [12]. Pneumonitis of grade 3 was considered a DLT in two patients after completion of the protocol therapy. The baseline CT scan of both patients taken before the protocol treatment revealed mild emphysematous, but no interstitial, changes. Radiation pneumonitis is the most common dose-limiting complication of TRT, with V20 being associated with the development of severe radiation pneumonitis [13–15]. Indeed, one of the two patients who manifested pneumonitis of grade 3 in our study had V20 values of >30 %. A previous study found that pneumonitis of grade 4 occurred in 6 % of elderly (>70 years of age) patients with NSCLC treated with chemoradiotherapy but in only 1 % of younger patients (P=0.02) [16]. indicating that elderly patients experience greater pulmonary toxicity. The toxic effects of concurrent chemoradiotherapy thus warrant close monitoring in elderly patients because of the increased incidence of pulmonary toxicity.

The standard administration schedule of S-1 alone is treatment for 4 weeks followed by a 2-week rest [6]. Compared with this schedule, drug administration for 2 weeks followed by a 1-week rest was found to be more feasible without a decrease in dose intensity or antitumor efficacy in patients with advanced head and neck cancer [17]. On the basis of these findings, we adopted a schedule of S-1 administration for 2 weeks followed by a 1-week rest in the present study, and we found that the dose intensity of S-1 was well maintained when the drug was administered in combination with TRT in elderly patients. A previous phase I study of S-1 with concurrent TRT in elderly patients with locally advanced NSCLC was conducted by the Okayama Lung Cancer Study Group (OLCSG) [18]. The treatment schedule of S-1 in this previous study consisted of 2 weeks on and 2 weeks off. The OLCSG study also determined the RD of S-1 to be 80 mg m^{-2} day^{-1}, consistent with our present data. Together, these observations indicate that the full single-agent dose of S-1 can be combined with concurrent TRT in elderly patients with locally advanced NSCLC.

A recent phase III study of TRT with or without daily carboplatin for elderly (≥70 years of age) patients with locally advanced NSCLC found that overall survival was significantly longer for the chemoradiotherapy group than for the TRT-only group (22.4 versus 16.9 months; P= 0.0179) [19]. suggesting that such patients should be encouraged to receive combined-modality therapy. Although tumor evaluation was not the primary objective of the present study, and the small sample size precludes any definitive conclusions regarding treatment efficacy, the response rate of 83.3 % with a median survival time of 34.0 months is promising. Given its efficacy and favorable toxicity profile, oral S-1 combined with concurrent TRT warrants further clinical investigation for elderly patients with locally advanced NSCLC.

Conflicts of interest

The authors declare no actual or potential conflicts of interest.

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