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PHASE I STUDIES

Phase I study of S-1 plus paclitaxel combination therapy as a first-line treatment in elderly patients with advanced non-small cell lung cancer

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Summary

This phase I study was aimed at determining the maximum tolerated dose (MTD) and recommended dose (RD) for oral S-1 plus paclitaxel combination therapy in elderly patients with non-small cell lung cancer (NSCLC). Chemotherapy-naïve patients (age, >70 years) with stage III/IV NSCLC were treated with paclitaxel intravenously at four dose levels (DLs), 60, 70, 80, and 90 mg/m^2, on day 1 and 8, and with S-1 (80 mg/m^2) orally on days 1–14 every 3 weeks. MTD was defined as the dose at which two of the initial three patients experienced dose-limiting toxicities (DLTs). Three patients were added when the initial three patients experienced DLTs. The dose administered in three of the six patients with DLTs met the definition of MTD. The RD was defined as a dose 1 DL below the MTD. Fifteen patients including six on DL 1 and three each on DLs 2, 3, and 4 were enrolled. One patient experienced a DLT (febrile neutropenia) at DL 1. The remaining DLTs were noted at DL 4 (in one patient each): febrile neutropenia, grade (G) 3 skin rash, G3 diarrhea, G3 stomatitis, and G3 international normalized ratio (INR) elevation. The MTD of paclitaxel was 90 mg/m^2. The RD for both S-1 and paclitaxel was 80 mg/m^2 (DL 3). The response rate was 45.5% (8 of 15 patients achieved a partial response). In conclusion, the RD of both S-1 and paclitaxel was 80 mg/m^2 in the combination therapy for chemotherapy-naïve patients with advanced NSCLC.

Keywords S1 · Paclitaxel · Non-small cell lung cancer · Combination chemotherapy

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and the number of elderly patients with lung cancer continues to increase. Approximately 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), and nearly 50% are aged ≥70 years [1]. Based on prospective randomized controlled trials for elderly patients with NSCLC, the current standard chemotherapy for those with no driver mutations is monotherapy with cytotoxic drugs such as docetaxel (DOC) or vinorelbine (VNR). However, the overall response rate (ORR) to these single agents remains 10–20% at most [2]. The superiority of platinum-based combination chemotherapy versus single-agent chemotherapy and the safety and effectiveness of non-platinum combination chemotherapy remain controversial. Therefore, development of effective chemotherapy for elderly patients with NSCLC is warranted.

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S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) is an oral fluoropyrimidine comprising tegafur (a prodrug of 5-fluorouracil [5-FU]), 5-chloro-2,4-dihydroxy-pyridine (CDHP), and potassium oxonate at a molar ratio of 1:0.4:1. CDHP increases the plasma concentration of 5-FU by inhibiting dihydropyrimidine dehydrogenase while oxonate inhibits the phosphorylation of 5-FU and reduces its gastrointestinal toxicities. Thus, S-1 has been designed to enhance the antitumor activity of 5-FU while reducing its gastrointestinal toxicity. In a phase II trial of S-1 monotherapy in previously untreated patients with advanced NSCLC, the ORR was 22% and the median survival time (MST) was 10.2 months [3].

Paclitaxel is a taxane drug that targets microtubules. It binds to and stabilizes microtubules, which enhances tubulin polymerization and inhibits spindle fiber function, resulting in the inhibition of mitosis and cell division. In a phase II trial involving paclitaxel infusion for 3 h in patients with previously untreated stage III and IV NSCLC, the ORR was 32% and the MST was 7 months [4].

Thymidine phosphorylase converts 5-FU to its more active form, fluorodeoxyuridylate, and a correlation between the expression of thymidine phosphorylase and efficacy of 5-FU–based chemotherapy has been observed [5]. Paclitaxel upregulated the expression of thymidine phosphorylase mRNA in human gastric cancer xenografts [6]. These results suggest the possibility of a synergistic effect of the S-1 and paclitaxel combination. Nukatsuka et al. found that the combination of paclitaxel and S-1 synergistically reduced tumor mass in a mouse model of human breast cancer [7]. Furthermore, in several phase II studies, the S-1 plus paclitaxel combination was effective and tolerated by patients with advanced gastric cancer [8–10], and a retrospective study by Aono et al. showed that S-1 and paclitaxel combination therapy is effective for pretreated advanced NSCLC, with a response rate of 32.6% and median PFS of 253 days [11].

The above-mentioned studies indicate that the combination of S-1 and paclitaxel might be effective for the treatment of elderly patients with NSCLC; however, the safety of this combination in elderly patients is unclear. Hence, we performed a phase I study of oral S-1 combined with weekly paclitaxel in elderly patients with advanced NSCLC to determine the maximum tolerated dose (MTD) and recommended dose (RD).

Patients and methods

Patient eligibility

Patients who fulfilled the following eligibility criteria were registered: at least one measurable tumor lesion, cytologically or histologically confirmed NSCLC, stage IIIB disease without any indications for radiotherapy or stage IV disease, no prior chemotherapy, age of ≥70 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, adequate organ function and bone marrow activity (neutrophil count, ≥3000/μL; platelet count, ≥100,000/μL; hemoglobin level, ≥9.5 g/dL; serum bilirubin concentration, ≤1.5 mg/dL; serum aspartate aminotransferase and alanine aminotransferase concentrations, ≤twice the upper limit of the normal range; creatinine level, ≤upper limit of normal; and creatinine clearance rate, ≥60 mL/min), life expectancy of >2 months, and ability to take medications orally. All patients had to provide written informed consent. The trial was approved by the Ethics Committee of the Kyoto Prefectural University of Medicine, Kyoto, Japan (RBMR-C-449). The trial was supervised and managed by the Ethics Committee.

Patients were excluded from the study if they had interstitial pneumonia, a severe concomitant disease (e.g., severe cardiac disease, uncontrolled diabetes, or severe infection), an active concomitant malignancy, severe drug hypersensitivity, or alcohol hypersensitivity. In addition, patients were excluded if they had received flucytosine.

Treatment plan and dose-escalation schedule

S-1 was orally administered twice a day on days 1–14, followed by a 7-day rest period. The dose of S-1 (80 $mg \cdot m^{(2)-1} \cdot day^{-1}$) was calculated according to the body surface area as follows: 40, 50, and 60 mg of S-1 for body surface areas of <1.25, 1.25–1.50, and ≥1.50 m^2, respectively. Four dose levels (DLs) of paclitaxel (DL 1–4) were evaluated: 60, 70, 80, and 90 mg/m^2, respectively. Paclitaxel was administered intravenously on day 1 and 8. The combination treatment was repeated every 3 weeks.

Dose-limiting toxicities (DLTs) were defined as any of the following: (i) febrile neutropenia, (ii) grade 4 (G4) neutropenia or leukopenia for ≥3 days, (iii) G4 thrombocytopenia, (iv) neuropathy of grade ≥ G3, (v) nonhematological adverse events (except nausea, vomiting, and alopecia) of grade ≥ G3, (vi) delay in paclitaxel infusion on day 8, and (vii) delay of >2 weeks in the administration of the next course of treatment.

Dose escalation followed a standard 3 + 3 design and was based on the toxicity during the first cycle of chemotherapy. If no DLTs were observed in the initial three patients at a predefined DL, the dose of paclitaxel was increased to the next DL. If at least two of the initial three patients experienced a DLT at a particular DL, enrollment was stopped at that DL. If one of the three patients experienced a DLT, an additional three patients were enrolled at the same DL. If one or two of the six patients experienced DLTs at a particular DL, recruitment started at the next DL. If at least three of the six patients experienced DLTs at a particular DL, enrollment was stopped at that DL, which was defined as the MTD. The preceding DL was designated as the RD.

Study assessment

Complete blood cell counts and chemistry panels were performed at least once weekly. Computed tomography or magnetic resonance imaging scanning was performed monthly to evaluate the anticancer effect of the combination treatment. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

The primary endpoint of this study was the determination of the MTD and RD. The secondary endpoints were safety and ORR. All analyses were performed using the JMP software program version 8.0 for Windows.

Results

Patient characteristics

Fifteen patients were enrolled from July 2008 through January 2010. The patient characteristics are summarized in Table 1. The median age of the patients was 77 (range, 72–84) years. Nine and six patients were men and women, respectively. Four patients had an ECOG PS of 1; seven, five, and three patients had adenocarcinoma, squamous cell carcinoma, and NSCLC, respectively. Eleven patients had stage IV disease, and epidermal growth factor receptor (*EGFR*)-sensitive mutations were detected in four patients.

Table 1 Patients characteristics

Number of patients	15
Age (years)	
Median	77
Range	72–84
Sex	
Male	9
Female	6
Performance status	
0	11
1	4
Histology	
Adenocarcinoma	7
Squamous cell carcinoma	5
not other specified	3
Stage	
IIIB	4
IV	11
EGFR mutation status	
Positive	4
Negative	6
Unknown	5
Smoking history	
Yes	11
No	4

MTD, RD, and toxicity

The number of registered patients and DLTs at each DL are listed in Table 2. All toxicities are listed in Table 3. At DL 1, one patient experienced a DLT (G3 febrile neutropenia) while at DLs 2 and 3, no DLTs were observed. Finally, two of the three patients experienced DLTs at DL 4: one had G3 febrile neutropenia and G3 skin rash, and the other had G3 diarrhea, G3 stomatitis, and G3 INR elevation. One patient had G2 interstitial lung disease. No treatment-related deaths (TRDs) were observed at any DL. Since the MTD was determined to be DL 4, 80 mg/m^2 paclitaxel and 80 mg/m^2 oral S-1 at DL 3 was confirmed as the RD for phase II (ongoing).

Efficacy

All patients were assessable for responses in this phase I study. The response rates are shown in Table 4. Eight, six, and one patient showed a partial response, stable disease, and progressive disease, respectively. The ORR was 45.5% (95% confidence interval [CI], 26.9–65.3), and the disease control rate was 90.9% (95% CI, 72.2–97.5).

Discussion

Non-platinum monotherapy has been effective in the treatment of NSCLC in the elderly. For instance, in the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) trial, elderly patients with advanced NSCLC treated with VNR monotherapy had higher survival rates and better quality of life scores than those of the patients who received the best supportive care (BSC; median survival time, 28 versus 21 weeks) [12]. The West Japan Thoracic Oncology Group Trial (WJTOG9904) compared DOC monotherapy with VNR monotherapy in elderly patients with advanced NSCLC. Although DOC did not significantly improve the median survival time (14.3 versus 9.9 months), it improves progression-free survival (PFS; 5.5 versus 3.1 months) and response rate (22.7% versus 9.9%) [2].

Prospective studies of platinum-doublet chemotherapies in elderly patients have also been performed. Quoix et al. [12] performed a phase III study comparing carboplatin plus

Table 2 Dose escalation schedule and dose-limiting toxicities (DLTs) observed at each dose level (DL)

Level	n	Paclitaxel (mg/m^2)	DLTs		
1	6	60	Febrile neutropenia $n = 1$	Body surface area	TS-1(mg/day)
2	3	70		1.25	80
3	3	80		1.25–1.5	100
4	3	90	Febrile neutropenia and grade 3 (G3) skin rash, G3 stomatitis $n = 1$	>1.5	120
			G3 diarrhea and G3 stomatitis, G3 international normalized ratio (INR) elevation $n = 1$		

weekly paclitaxel (CP) with monotherapy (VNR or gemcitabine) in elderly patients (IFCT-0501). This study demonstrated the superior efficacy of the CP regimen (overall survival of 10.3 vs 6.2 months); however, the TRD rate in the platinum arm was as high as 4.4% [13]. In Japan, a phase III study comparing cisplatin plus weekly DOC combination therapy to DOC monotherapy (JCOG0803/WJOG4307) in elderly patients failed to demonstrate any survival advantage for those receiving cisplatin plus weekly DOC monotherapy [14]. Considering the above results, platinum combination therapy is not suitable for the elderly in Japan.

Researchers have considered the benefits of non-platinum monotherapy versus non-platinum combination therapies. Gridelli et al. [14] conducted a clinical study comparing the effectiveness and toxicity of VNR plus gemcitabine combination therapy to those of monotherapies administered to elderly patients in the Multicenter Italian Lung Cancer in the Elderly Study (MILES) trial. They found that the combination treatment did not improve survival and was more toxic than either drug administered alone [15]. Based on the results of the above studies, the current standard chemotherapy for elderly patients is the use of a single cytotoxic drug such as DOC or VNR.

Recently, other non-platinum combination chemotherapies have shown promising results in elderly patients. For example, a phase I/II study found that S-1 and gemcitabine are efficacious and have acceptable toxicity [16]. Moreover, Pino et al. [16] reported that the combination of biweekly paclitaxel and gemcitabine is well tolerated [17].

Table 3 All adverse events at each dose level (DL)

Adverse Event	Level 1 ($n = 6$)		Level 2 ($n = 3$)		Level 3 ($n = 3$)		Level 4 ($n = 3$)	
	Any	G3/4	Any	G3/4	Any	G3/4	Any	G3/4
Hematological								
Leukopenia	3	1/1	1	0/0	3	3/0	3	2/1
Neutropenia	5	1/0	2	0/0	3	2/0	3	2/0
Thrombocytopenia	4	0/0	1	0/0	2	0/0	3	0/0
Anemia	5	0/0	3	0/0	3	1/0	3	0/0
Non-hematological								
Nausea/vomitting	5	0/0	2	0/0	1	0/0	0	0/0
Hepatic dysfunction	1	0/0	1	0/0	1	0/0	1	0/0
Renal dysfunction	0	0/0	2	0/0	2	0/0	2	0/0
Stomatitis	2	0/0	2	2/0	3	0/0	3	2/0
Diarrhea	4	0/0	2	0/0	2	0/0		1/0
Constipation	2	0/0	1	0/0	2	0/0	2	0/0
Peripheral nueropathy	2	0/0	0	0/0	1	0/0	2	0/0
Taste alternation	3	–	2	–	0	–	1	–
Alopecia	5	–	2	–	3	–	2	–
Hiccoughs	0	0/–	0	0/–	2	0/–	1	0/–
Skin rash	0	0/0	0	0/0	0	0/0	1	1/0
Pneumonitis	1	0/0	0	0/0	0	0/0	0	0/0
INR elevation	0	0/–	0	0/–	0	0/–	1	1/–
Febrile nuetropenia	–	1/0	–	0/0	–	0/0	1	1/0

INR international normalized ratio

Table 4 Efficacy

Response	Dose level				
	Dose level 1 $n=6$	Dose level 2 $n=3$	Dose level 3 $n=3$	Dose level 4 $n=3$	Total $n=15$
CR	0	0	0	0	0
PR	2	2	2	2	8
SD	4	0	1	1	6
PD	0	1	0	0	1
Response rate (%)	45.5% (95% CI, 26.9–65.3)				
Disease control rate (%)	90.9% (95% CI, 72.2–97.5)				

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CI* confidence interval

We demonstrated the safety of the S-1 and paclitaxel combination for elderly patients in our present study. The DLTs were febrile neutropenia and G3 skin rash, stomatitis, diarrhea, and INR elevation. The major hematological toxicities were leukopenia and neutropenia whereas the major non-hematological toxicities were stomatitis and diarrhea. Only five patients experienced G1 peripheral neuropathy.

In our study, S-1 was administered on days 1–14, and paclitaxel was administered intravenously on day 1 and 8 every 3 weeks. The regimen we adopted was used in a phase II study in patients with gastric cancer (OGSG0105). The study showed high efficacy (response rate of 48% and a median survival time of 13.9 months) with tolerable toxicity. In this study, no G4 toxicities were observed [18]. Although peripheral neuropathy is frequently observed as an adverse effect of paclitaxel, Fidias et al. [18] reported that patients administered 90 mg/mm^3 weekly paclitaxel had a lower risk of peripheral neuropathy than that in patients who received high-dose weekly paclitaxel [19]. In addition, Rossi et al. [19] determined that the primary toxicity of weekly paclitaxel in elderly patients (≥70 years) with advanced NSCLC was G2/3 asthenia; no other G3/4 toxicities were reported in their prospective phase II study [20]. Furthermore, the prospective study by Goto et al. [20] showed that 2 weeks of S-1 monotherapy followed by a 1-week S-1-free interval maintains efficacy and is well tolerated in elderly patients with NSCLC [21]. The treatment schedule we adopted in this study may be one of the reasons why the S-1/paclitaxel combination was tolerated by the elderly patients.

A retrospective study by Aono et al. showed that S-1 and paclitaxel combination therapy is effective for pretreated advanced NSCLC, with a response rate of 32.6% and median PFS of 253 days [11]. In this retrospective study, S-1 was administered on days 1–14 and paclitaxel was administered intravenously on day 1 and 15 every 4 weeks. The major G3/4 toxicity was neutropenia (30.4%). Although paclitaxel was administered in our study every 3 weeks, there was no increase in the incidence of G3/4 neutropenia (rate, 33.3%). The response rate in our study (45.5%) was higher than that in a retrospective study [11] because of a different schedule of paclitaxel administration and selection bias in the patients registered retrospectively.

In conclusion, we demonstrated that the combination of S-1 and weekly paclitaxel is feasible and may be useful in elderly patients. We determined that the RD for the S-1 and paclitaxel combination regimen was 80 mg/m^2 for both agents. In the phase II portion of this study (ongoing), we will confirm the ORR and survival benefit afforded by the RD.

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Compliance with ethical standards

Conflicts of interests J Uchino reports grants from Eli Lilly Japan K.K., outside the submitted work. T Yamada reports grants from Nippon Boehringer Ingelheim Co., Ltd., and Ono Pharmaceutical Co., Ltd., outside the submitted work. K Takayama reports grants from Chugai-Roche Co., grants from Ono Pharmaceutical Co., personal fees from Astrazeneca Co., personal fees from Chugai-Roche Co., personal fees from MSD-Merck Co., personal fees from Eli Lilly Co., personal fees from Boehringer-Ingelheim Co., personal fees from Daiichi-Sankyo Co., outside the submitted work. The other authors have no conflict of interest to declare.

Ethical approval All procedures performed in human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

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