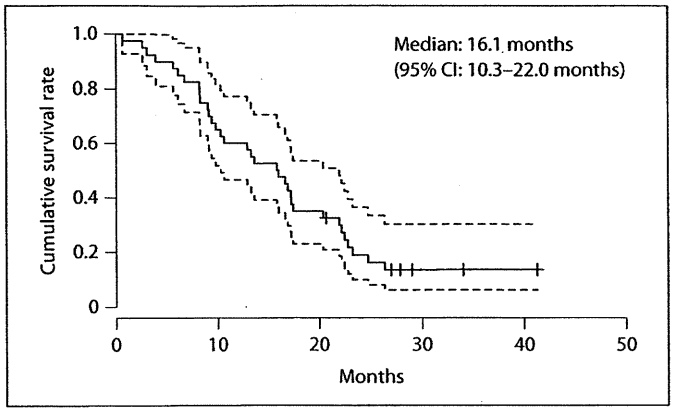

Fig. 1. Overall survival, median 16.1 months (95% CI, 10.3–22.0 months).

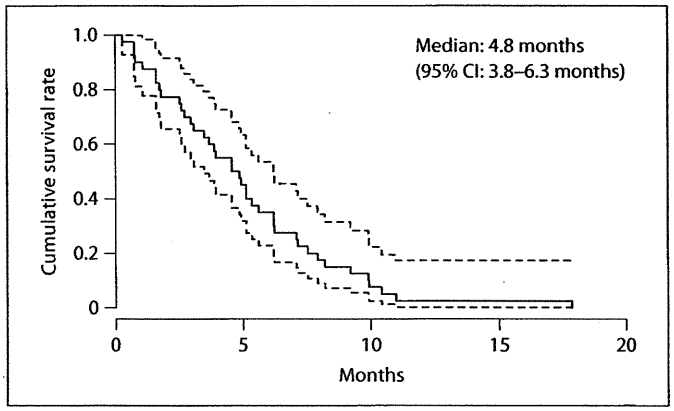

Fig. 2. PFS, median 4.8 months (95% CI, 3.8–6.3 months).

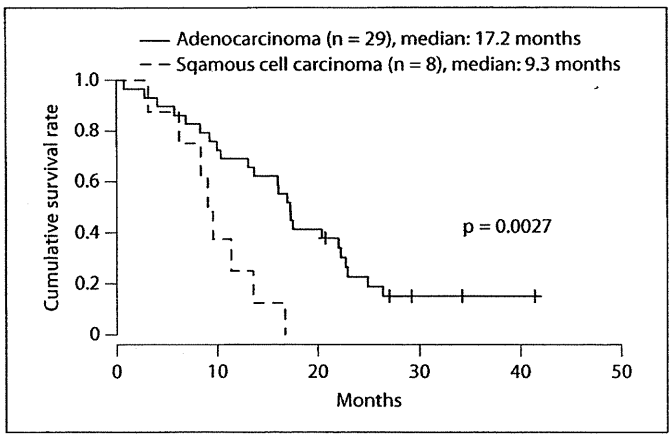

Fig. 3. Overall survival by histological type, median 17.2 months (95% CI, 13.7–22.7 months) for adenocarcinoma and 9.3 months (95% CI could not be determined) for squamous cell carcinoma.

rolled patients were 16.1 months (95% CI, 10.3–22.0 months) and 4.8 months (95% CI, 3.8–6.3 months), respectively (fig. 1, 2). One-year survival rate was 60.0% (95% CI, 43.3–75.1%).

We then conducted post-hoc analysis to evaluate differences in efficacy outcomes between histological types. ORRs were 34.5% (95% CI, 17.9–54.3%) in adenocarcinoma (n = 29) and 12.5% (95% CI, 0.3–52.7%) in squamous cell carcinoma (n = 8). In addition, the adenocarcinoma group showed an MST of 17.2 months (95% CI, 13.7–22.7 months), whereas the squamous cell carcinoma group had an MST of 9.3 months (95% CI, could not be determined). The Kaplan-Meier plot of OS by histological type is shown in figure 3.

Toxicity Profiles

Severe adverse events were uncommon and were manageable in most cases. Overall, the most common hematological adverse events were leukopenia (60.0%), neutropenia (55.0%), anemia (70.0%), and thrombocytopenia (20.0%), while the most common nonhematological adverse events were diarrhea (62.5%), nausea (50.0%), and anorexia (62.5%). Stomatitis was of grade 1 to grade 2 in severity (grade 1, 3 cases; grade 2, 1 case). Hematological toxicities of grade 3 or 4 included leukopenia (10.0%), neutropenia (32.5%) and anemia (5.0%). The most common nonhematological toxicities of grade 3 or 4 included diarrhea (15.0%), nausea (7.5%), and anorexia (17.5%) (table 4). Grade 2 interstitial lung disease was reported in 1 patient, resolving after termination of the protocol treatment. Subsequently, no treatment-related deaths were encountered.

Treatment after Protocol Discontinuation

Although any treatment was permitted, the majority of enrolled patients received a platinum-based regimen as a second-line treatment. Twenty-two patients (55.0%) received carboplatin plus paclitaxel, and 3 patients (7.5%) received carboplatin plus docetaxel. Four patients (10.0%) showed sensitive *EGFR* mutation, and all 4 received second-line gefitinib monotherapy, resulting in SD response.

UGT1A1 Genotype Analysis and Association with Toxicity

The 40 patients included 1 patient homozygous and 8 patients heterozygous for *UGT1A1*6* compared to 7 patients heterozygous for *UGT1A1*28*. No patients showed both genotypes. Patients who were homo- or hetero-

Table 3. Overall response

Response	n	%
CR	0	0
PR	12	30
SD	17	42.5
Progressive disease	9	22.5
Not evaluable	2	5.0

Response rate: 30% (95% CI, 16.6–46.5%).
Disease control rate: 72.5% (95% CI, 56.1–85.4%).

Table 4. Toxicity for all cycles

	Grade				Grade ≥3, %
	1	2	3	4	
Leukopenia	9	11	4	0	10.0
Neutropenia	5	4	12	1	32.5
Anemia	14	12	2	0	5.0
Thrombocytopenia	7	1	0	0	0
Diarrhea	12	7	6	0	15.0
Nausea	10	7	3	0	7.5
Vomiting	2	3	1	0	2.5
Anorexia	13	5	7	0	17.5

zygous for *UGTA1A*6* showed a trend toward a high incidence of grade 3 diarrhea (p = 0.055). No relationship was identified between grade 3 or 4 neutropenia and *UGT1A1*6* (p = 0.32). The patient harboring homozygous *UGTA1A*6* showed grade 3 neutropenia and diarrhea. No association of *UGT1A1*28* with severe toxicity was observed. The grade 2 interstitial lung disease developed in a patient heterozygous for *UGT1A1*28*.

Discussion

There is an obvious need for equally active but better-tolerated regimens to optimize therapy for advanced NSCLC. This phase II trial employing irinotecan plus S-1 as a first-line therapy for chemotherapy-naïve NSCLC revealed a promising RR of 30% and an MST of 16.1 months, although the primary endpoint of ORR was not met. Furthermore, toxicity was manageable overall, with low frequencies of grade 3 or 4 hematological and non-hematological toxicities including neutropenia, diarrhea, nausea, and anorexia. Collectively, the present study demonstrated irinotecan plus S-1 as a promising and well-tolerated regimen for first-line treatment of advanced NSCLC.

Of note was the finding that utilizing combination therapy, RR and MST were significantly inefficacious against squamous cell carcinoma compared to adenocarcinoma. A previous study found no significant difference in PFS or RR with cisplatin plus S-1 by histological type [20]. Irinotecan plus S-1 has been developed for gastrointestinal malignancies. A limited number of squamous cell carcinomas were treated in this study. So whether irinotecan plus S-1 is effective against nonadenocarcinoma histologies should be further evaluated.

Several randomized phase II trials have compared cisplatin-based therapy with cisplatin-free therapy in the first-line treatment setting. Docetaxel/gemcitabine and vinorelbine/cisplatin combinations showed similar efficacy (RR, 30.0 vs. 39.2%, respectively) and survival data (MST, 9.0 vs. 9.7 months, respectively), while the cisplatin-free regimen showed less toxicity [21]. Gemcitabine plus vinorelbine was also compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine [22]. No significant differences in the primary endpoint of quality of life were seen between the platinum and nonplatinum arms, with comparable MSTs of 38 and 32 weeks, respectively. Subsequent meta-analysis showed that nonplatinum third-generation-based combination regimens offer comparable efficacy with less toxic profiles when compared with platinum-based regimens [23]. Our findings likewise showed that the efficacy of combined irinotecan and S-1 is equivalent to that of the reported platinum doublet regimens, although limitations exist in comparing results between different studies.

Two clinical trials using the S-1 and irinotecan combination for untreated NSCLC have recently been reported from Japan. In a phase I trial, patients with advanced NSCLC received S-1 (80 mg/m^2) on days 1–14 and irinotecan (50–80 mg/m^2) on days 1, 8 and 15 of each 4-week cycle. That study concluded by recommending 70 mg/m^2 as the weekly dose of irinotecan [24]. In the WJTOG 3505 phase II study, patients were treated with irinotecan at 150 mg/m^2 on day 1 and oral S-1 at 80 mg/m^2 on days 1–14 every 3 weeks. That study showed an ORR of 28.6%. Median PFS was 4.9 months, whereas median OS was 15 months, with favorable toxicity profiles [25]. Other nonplatinum regimens utilizing S-1 have also been reported, such as docetaxel plus S-1 or gemcitabine plus S-1 [26–29]. Efficacies were almost the same, although higher rates of myelosuppression with ≥grade 3 neutropenia were observed, particularly in the docetaxel plus S-1 arm.

A phase II trial of irinotecan and S-1 for advanced gastric cancer using the same treatment schedule as in the present study revealed good efficacy (RR, 54.2%) and dose intensity [16], which encouraged us to apply that schedule in the present study for NSCLC. Dose intensity in our study was 95% for S-1 and 95% for irinotecan, in line with the findings of the WJTOG 3505 study. Recently, the FIRIS study reported that PFS with irinotecan plus S-1 (IRIS) was not inferior to that with FOLFIRI (fluorouracil and folinic acid plus irinotecan) in a second-line treatment setting for metastatic colorectal cancer [30]. In that study, irinotecan was also administered on days 1 and 15 for the IRIS regimen. The best treatment schedule of irinotecan plus S-1 for lung cancer has yet to be determined, warranting further studies.

Determination of *UGT1A1* genotypes might be clinically useful for predicting severe toxicity by irinotecan. The presence of the *UGT1A1**6 allele was associated with severe grade 4 neutropenia compared with patients showing the reference genotype [18]. Genotypes either hetero- or homozygous for *UGT1A1**28 represent a significant risk factor for severe toxicity from irinotecan [19]. In this study, no association between *UGT1A1* genotypes and severe toxicity was observed. As the trial was powered for the primary endpoint, supplemental analyses were based on smaller numbers of patients and statistically meaningful analysis may thus have been precluded. Some prospective trials are underway to clarify whether reducing irinotecan dose is necessary for patients showing *UGT1A1* genotypes.

Various limitations to this study need to be considered. First, the majority of patients in this study had adenocarcinoma (73%). Patient selection could thus have contributed to survival outcomes. Second, EGFR mutation testing was performed for 17 patients, accounting for 42.5% of enrolled patients. We were therefore unable to assess the effects of EGFR mutation on OS. Finally, the study population was entirely Japanese, and the efficacy of this combination therapy thus may not be valid among non-Asian NSCLC patients.

In conclusion, the regimen of irinotecan and S-1 conferred similar survival benefits with good tolerability when compared with previously reported platinum-based regimens. This combination might represent an alternative to first-line chemotherapies for advanced NSCLC, and a more extensive clinical trial is warranted to verify the efficacy of this regimen.

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PHASE I STUDIES

Phase I dose-escalating study of panobinostat (LBH589) Administered intravenously to Japanese patients with advanced solid tumors

Sachi Morita · Satoshi Oizumi · Hironobu Minami · Koichi Kitagawa · Yoshito Komatsu · Yutaka Fujiwara · Megumi Inada · Satoshi Yuki · Naomi Kiyota · Ayako Mitsuma · Masataka Sawaki · Hiromi Tanii · Junko Kimura · Yuichi Ando

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Summary Panobinostat (LBH589) is a potent pan-histone deacetylase inhibitor. As a result of promising preclinical data, Phase I and II clinical trials of intravenous and oral panobinostat have been conducted in patients with a wide variety of hematologic and solid tumors. This is the first report of a phase I study to evaluate intravenous panobinostat given on days 1 and 8 of a 21-day cycle in patients with solid tumors. The primary objective was to characterize the safety and tolerability of panobinostat by evaluating the occurrence of dose-limiting toxicity (DLT) and determining the maximum tolerated dose (MTD) in Japanese patients with advanced solid tumors. Secondary objectives included characterizing the pharmacokinetics and assessing antitumor activity. Fourteen patients were assigned to three dose levels (Cohort 1: 10 mg/m^2 [three patients], Cohort 2: 15 mg/m^2 [three patients], Cohort 3: 20 mg/m^2 [eight patients]), according to a standard "3+3" design. One patient who received 20 mg/m^2 had a DLT (grade 3 elevation of γ-glutamyl transpeptidase for >7 days). Thrombocytopenia was observed in all patients (grade 3 or 4 in 8), the severity of which was dependent on the dose and platelet count at baseline. The thrombocytopenia rapidly resolved within 8 days. Plasma panobinostat levels increased dose dependently, without clinically significant drug accumulation. Stable disease for ≥4 months was observed in six patients; however, there were no complete or partial responses. It is feasible to conclude that 20 mg/m^2 was the MTD and recommend as the starting dose for phase II clinical trials.

This trial is registrated at www.clinicaltrials.gov as NCT00739414.

S. Morita · K. Kitagawa · M. Inada · A. Mitsuma · M. Sawaki · Y. Ando (✉)
Department of Clinical Oncology and Chemotherapy,
Nagoya University Hospital,
65 Tsurumai-cho, Showa-ku,
Nagoya, Aichi 466-8560, Japan
e-mail: yando@med.nagoya-u.ac.jp

S. Oizumi
First Department of Medicine,
Hokkaido University School of Medicine,
North 15, West 7, Kita-ku,
Sapporo, Japan

H. Minami · Y. Fujiwara · N. Kiyota
Medical Oncology/Hematology, Department of Medicine,
Kobe University Hospital & Graduate School of Medicine,
7-5-2, Kusunoki-cho, Chuo-ku,
Kobe, Japan

Y. Komatsu
Department of Cancer Chemotherapy,
Hokkaido University Hospital Cancer Center,
North 14, West 5, Kita-ku,
Sapporo, Japan

S. Yuki
Third Department of Internal Medicine,
Hokkaido University School of Medicine,
North 15, West 7, Kita-ku,
Sapporo, Japan

H. Tanii
Novartis Pharma KK, Translational Science,
12-24, Nishi-Azabu 4-chome, Minato-ku,
Tokyo, Japan

J. Kimura
Novartis Pharma KK, Oncology Translational Medicine,
12-24, Nishi-Azabu 4-chome, Minato-ku,
Tokyo, Japan

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Introduction

Histone deacetylase (HDAC) inhibitors are a novel class of anticancer agents that inhibit HDACs involved in the deacetylation of histone and non-histone proteins [1, 2]. In humans, 18 HDACs have been identified and grouped into four classes according to their homology to yeast proteins [1–4]. Class I, II and IV HDACs contain a zinc (Zn) molecule in their active site [1–4]. Class I HDACs are localized within the cell nucleus and show high enzymatic activity toward histone substrates [1–4]. Class II HDACs act mainly on non-histone proteins [2]. Class IV HDAC has features of both class I and II [2]. Class III HDACs consist of the NAD-dependent sirtuin family, do not contain Zn and are not inhibited by any current HDAC inhibitors [1–4]. Cancer cells have high levels of expression of HDACs, resulting in hypoacetylation of histones [4]. In many tumor cell lines, inhibition or down-regulation of HDACs leads to cell-cycle arrest and differentiation, thereby inducing apoptosis [4]. HDAC inhibitors are broadly classified as class I specific inhibitors or pan-histone deacetylase (pan-HDAC) inhibitors against all class I, II and IV HDACs. Several HDAC inhibitors have been undergoing clinical development in recent years [1, 2]. Among the pan-HDAC inhibitors, vorinostat (suberoylanilide hydroxamic acid, SAHA) has been approved by the United States Food and Drug Administration (US FDA) for the treatment of cutaneous T-cell lymphoma (CTCL). More recently, romidepsin (depsipeptide, FK228), a class I specific HDAC inhibitor, was also approved by US FDA for CTCL.

Panobinostat (LBH589) is a potent pan-HDAC inhibitor [1, 2], belonging to the structurally new cinnamic hydroxamic acid class of compounds [1]. As a pan-HDAC inhibitor, panobinostat is at least 10-fold more potent than vorinostat in vitro [2]. As a result of promising preclinical data, Phase I and II clinical trials of intravenous and oral panobinostat have been conducted in patients with a wide variety of hematologic and solid tumors [1, 2].

Two phase I studies of panobinostat given intravenously on consecutive days have been performed in Western patients with solid or hematologic malignancies [5, 6]. However, because of unexpected severe cases of QT interval prolongation corrected for heart rate by Fridericia's formula (QTcF), the treatment schedule of one study was modified to once weekly on days 1, 8, and 15 of a 28-day cycle, and the other trial was terminated [5, 6]. Once-weekly treatment of panobisnostat reduced the occurrence of QTcF prolongation. However, many patients who were treated for a 28-day cycle at the maximum tolerated dose (MTD) of 20 mg/m^2 required dose delays and reductions due to thrombocytopenia on day 15 [5]. Therefore, for this study, a new dosing schedule wherein panobinostat was given on days 1 and 8 of a 21-day cycle was utilized.

This study was an open-label, multicenter Phase IA dose-escalation study of intravenous panobinostat. This will be the first reported evaluation of panobinostat on a new weekly schedule, given on days 1 and 8 of a 21-day cycle. The primary objective was to characterize the safety and tolerability of panobinostat as a single agent, including an assessment of the occurrence of dose-limiting toxicity (DLT) and the determination of MTD, in adult Japanese patients with advanced solid tumors. Secondary objectives included characterizing the pharmacokinetic profile of panobinostat and evaluating antitumor activity.

Materials and method

Eligibility criteria

Patients with histologically or cytologically confirmed, advanced solid tumors who had progressive disease that did not respond to available standard therapies or for whom no standard therapy was available were enrolled. Additional eligibility criteria for enrollment included: having at least one measurable or non-measurable lesion; being ≥20 years; having an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2; having a life expectancy of ≥12 weeks; and having the following laboratory values: absolute neutrophil count ≥1,500/mm^3, hemoglobin ≥9 g/dl, platelets ≥100,000/mm^3, potassium ≥ the lower limit of normal (LLN) or correctable with supplements, total calcium (corrected for serum albumin) ≥ LLN or correctable with supplements, magnesium ≥ LLN or correctable with supplements, phosphorus ≥ LLN or correctable with supplements, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×the upper limit of normal (ULN) or ≤5.0×ULN if liver metastases were present, serum bilirubin ≤1.5×ULN, serum creatinine ≤1.5×ULN or 24-h creatinine clearance ≥50 ml/min, and being clinically euthyroid (thyroid stimulating hormone and free T4 within their respective normal ranges). Patients with evidence of central nervous system tumors or metastases, any peripheral neuropathy of ≥ grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE), impaired cardiac function, or other uncontrolled medical conditions were excluded. Patients who were receiving medications potentially associated with prolongation of the QT interval that could not be discontinued or switched to a different medication before starting treatment with the study drug were also excluded. Women of childbearing potential must have had negative results from a pregnancy test

performed 7 days before administration of panobinostat. The protocol and informed consent form were approved by the Institutional Review Board before study initiation. Written informed consent was obtained from all patients. The study was designed and implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, the guidelines of the Japanese Ministry of Health, Labor and Welfare, and the ethical principles laid down in the Declaration of Helsinki.

Study design and treatment plan

Study design Patients were recruited into three cohorts according to the standard "3+3" method (Cohort 1: 10 mg/m^2, Cohort 2: 15 mg/m^2, Cohort 3: 20 mg/m^2). Decisions regarding dose escalation were based on the safety profile, particularly occurrence of DLT during the first cycle of treatment for each patient. The population for determination of MTD consisted of patients who received both scheduled doses during Cycle 1 and completed all safety evaluations for at least 21 days or patients who experienced a DLT during Cycle 1. Patients who did not meet these requirements (e.g. patients who received only one dose of panobinostat during cycle 1) were included in the full analysis but regarded as ineligible for the determination of MTD and replaced. An event would be classified as a DLT if any of the following criteria were met: CTCAE grade 3 or 4 neutropenia lasting for >7 days, neutropenic fever; CTCAE grade 3 thrombocytopenia lasting for >7 days, any CTCAE grade 4 thrombocytopenia; CTCAE grade 2 neurotoxicity lasting for >7 days, ≥CTCAE grade 3 neurotoxicity; ≥CTCAE grade 3 cardiac general adverse events; ≥CTCAE grade 3 vomiting or ≥ CTCAE grade 3 nausea despite the use of optimal antiemetics; ≥CTCAE grade 3 diarrhea despite the use of optimal antidiarrheal treatments; other CTCAE grade 3 adverse events (excluding alkaline phosphatase) with a duration >7 days or CTCAE grade 4 adverse events (excluding alkaline phosphatase); or any other adverse event requiring a dose delay of longer than 7 days from the next scheduled dosing date. If all three patients did not experience a DLT, a new cohort of three patients was enrolled at the subsequent dose level. If one of the three patients had a DLT, the cohort was expanded to include a total of six patients. If no additional DLT occurred, a new cohort of three patients was enrolled at the subsequent dose level. If two or more patients had a DLT at any dose level, the cohort would be stopped and the lower dose cohort immediately preceding the cohort where DLTs were observed would be expanded to six patients to confirm the safety of that dose as the MTD.

Treatment plan Patients were given panobinostat intravenously over the course of 30 min once daily on days 1 and 8 of a 21-day cycle. For administration, panobinostat was dissolved in a solution of 5% dextrose in water to an appropriate concentration to achieve the dose required by body surface area. The final volume of the solution was 50 ml.

The treatment of panobinostat was stopped if the patient had any ≥ CTCAE grade 2 cardiovascular toxicity or any ≥ CTCAE grade 3 toxicity. If panobinostat could not be administered on day 8 (+3 days) during a treatment cycle, no further attempt was made to administer panobinostat during that cycle. If the start of the next cycle was delayed by more than 7 days, treatment with panobinostat was discontinued.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were collected from each patient during cycle 1. The samples were taken 0, 0.5, 0.75, 1, 2, 3, 5, 7, 24, 48, and 168 h after treatment on days 1 and 8.

Panobinostat concentrations in plasma samples were assayed using a validated liquid chromatography–tandem mass spectrometry assay. The lower limit of quantification was 0.5 ng/mL when 0.100 ml of human plasma was assayed. Panobinostat concentrations below the lower limit of quantification were treated as 0.0 ng/mL.

Noncompartmental analysis was employed to calculate pharmacokinetic parameters based on the panobinostat concentration–time data, using WinNonlin® Professional, version 5.2 software (Pharsight Corporation, Mountain View, CA). Areas under the time-concentration curves (AUCs) were calculated using the linear trapezoidal method.

Follow-up and clinical evaluation

Patients in whom treatment was interrupted or permanently discontinued due to an adverse event or laboratory abnormality were followed up at least once a week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event. All patients were followed up for adverse events 28 days after the last dose of panobinostat. Adverse events were monitored and recorded in accordance with CTCAE, version 3.0.

All potential sites of tumor lesions were assessed at baseline by radiologic techniques. Lesions were measured in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Response was assessed ≤7 days before the completion of each cycle of chemotherapy, at the time of study treatment completion, and at other times at the discretion of the investigator. The best overall response in each patient was classified as complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD), or unknown (UNK). An evaluation of PR or CR required that changes in tumor

Table 1 Patients' demographic and tumor characteristics

Demographic Variable/Tumor characteristics		N=14
Sex -n	Female	5
	Male	9
Baseline age (years)	Median (range)	63.0 (43–75)
Baseline weight (kg)	Median (range)	53.0 (44.2–71.2)
Primary site of cancer: n	Colon	3
	Stomach	2
	Gall bladder	1
	Lung	1
	Oesophagus	1
	Ovary	1
	Peritoneum	1
	Soft tissue	1
	Other	3
Tumor Histology/ Cytology: n	Adenocarcinoma	7
	Sarcoma	2
	Adenoid cystic carcinoma	1
	Melanoma	1
	Squamous cell carcinoma	1
	Undifferentiated carcinoma	1
	Other	1

measurements were confirmed by repeated assessments performed no less than 4 weeks after the criteria for the response had first been met.

Statistical analysis

Since platelet counts on day 7 or 8 influenced the occurrence of dose delays and reductions during the 21-day schedule, correlations between the percentage decrease in platelet counts on day 7 or 8 with dose and pharmacokinetic parameters were performed. All analyses were performed with Windows Version SAS® 9.2 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

From July 10, 2008 through June 5, 2009, a total of 14 patients were enrolled (Table 1). Four patients who received a panobinostat dose of 20 mg/m^2 discontinued the study because of adverse events (n=2: adverse events were suspected to be related to the study drug in one patient and not related in the other) or withdrawal of consent (n=2: one was at cycle 2 and the other was at cycle 3). The remaining ten patients discontinued the study because of disease progression. The median duration of treatment was 109 days (range: 21–408).

Safety

After excluding two patients who received only one dose of panobinostat at 20 mg/m^2 during cycle 1 due to thrombocytopenia, the occurrence of DLT was assessed in the remaining 12 patients. During the study, one patient dosed at 20 mg/m^2 had drug-related liver function abnormality assessed as a DLT (grade 3 elevation of γ-glutamyl transpeptidase for >7 days). This adverse event occurred simultaneously with events of grade 3 elevation of AST and grade 2 elevation of ALT that resolved within 7 days. The two excluded patients recovered from thrombocytopenia within 7 days and continued the study drug treatment. General safety was assessed in all 14 patients. All 14 patients had one or more adverse event during treatment and the most common adverse events (>30% of the patients) were thrombocytopenia, leukopenia, neutropenia, nausea, stomatitis, vomiting, fatigue, fever, decreased appetite, hypoalbuminemia, and rash (Table 2).

Table 2 Adverse events (occurring >30% of the patients)

	10 mg/m^2 n=3		15 mg/m^2 n=3		20 mg/m^2 n=8	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Leukopenia	3	0	1	1	5	2
Neutropenia	2	0	1	1	5	3
Thrombocytopenia	3	1	3	2	8	5
Nausea	1	0	2	0	4	0
Stomatitis	2	0	1	0	3	0
Vomiting	1	0	1	0	3	0
Fatigue	2	0	2	1	3	1
Fever	0	0	1	0	4	0
Decreased appetite	1	0	2	1	5	0
Hypoalbuminemia	1	0	3	0	2	0
Rash	2	0	0	0	3	0

As for electrocardiographic abnormalities, one patient given 10 mg/m^2 had a >60 msec prolongation of the QT interval as compared with baseline value, but the corrected value (QTcF) remained within the normal range. The remaining 13 patients had no substantial electrocardiographic abnormalities.

All patients experienced ≥ grade 1 thrombocytopenia, with peaks reaching grade 3 in five patients and grade 4 in three patients (cycle ≥2). One of the three patients with grade 4 thrombocytopenia was in the 15 mg/m^2 cohort and the remaining 2 were in the 20 mg/m^2 cohort. One patient in each of these cohorts required platelet transfusions. Thrombocytopenia significantly depended on the dose and the platelet counts at baseline (Fig. 1a, rs=0.704, p=0.005; Fig. 1b, rs=0.798, p=0.0006 by Spearman's rank correlation coefficient, respectively). However, thrombocytopenia rapidly resolved within 8 days in all patients (Fig. 1c).

20 mg/m^2 was designated as the MTD in this study, without testing a higher dose. Although 20 mg/m^2 was considered acceptable as a starting dose for Japanese patients, three patients in the 20 mg/m^2 cohort required dose interruption or omission of the second dose of cycle 1 because of adverse events (primarily thrombocytopenia [n=2] and elevation of liver enzymes [n=1]); consequently, the relative dose intensity in the 20 mg/m^2 cohort was low (Table 3). As a result, further dose escalation was deemed inappropriate and the study was concluded.

Pharmacokinetics

Pharmacokinetic data was obtained in all 14 patients (Table 4). Plasma concentrations of panobinostat rapidly decreased after infusion, followed by the elimination phase. The half-life of the terminal phase was approximately 20 h. Systemic exposure of panobinostat increased in a dose dependent manner. The systemic clearance of panobinostat was moderate (40 to 60 L/h) for both days 1 and 8. The highest plasma concentration 168 h after administration was 2.3 ng/mL in the 15 mg/m^2 cohort. This value was less than 1/100 of the maximum plasma concentration (C_{max}).

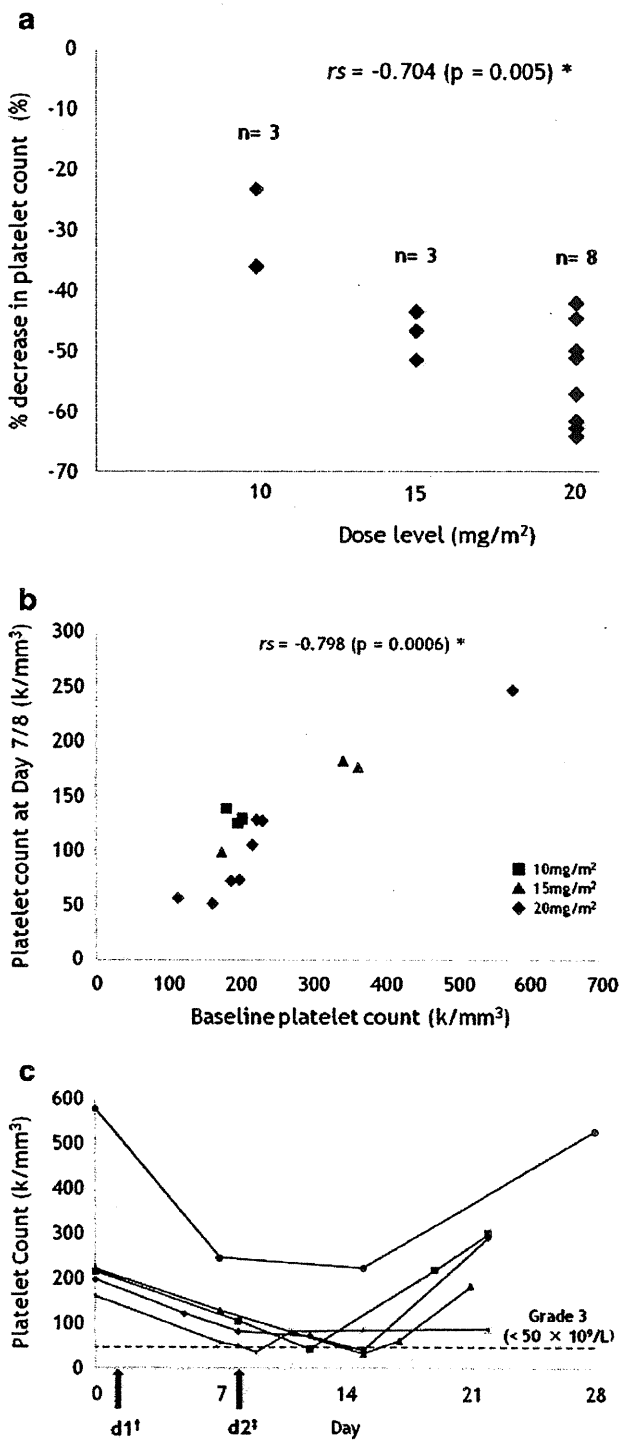

Fig. 1 **a**, percent decrease in platelet counts on day 7/8 according to dose level. The percent decrease was dose-dependent. **b**, scatter plot of baseline platelet counts versus platelet counts on day 7/8 during cycle 1. The platelet decrease appeared to correlate with the baseline counts. * *rs*: Spearman's rank correlation coefficient **c**, Time course of platelet counts during cycle 1 in five patients in the 20 mg/m^2 cohort who received both the 1st and 2nd doses. Three patients who received only the first dose during cycle 1 are excluded. (The second dose was not administered because of drug-related liver dysfunction in one patient and thrombocytopenia in the other two.) All patients recovered within 8 days after the second dose. The *dotted line* shows platelet count level of grade 3 (50×10^9/L). †d1: the 1st dose on day 1 of cycle 1 ‡d2: the 2nd dose on day 8 of cycle 1

Therefore, drug accumulation was considered negligible. Distribution of $AUC_{0\text{-}168}$ according to the dose level is shown in Fig. 2a. The severity of thrombocytopenia appeared to correlate with the $AUC_{0\text{-}168}$ (rs= −0.437, Fig. 2b) and the C_{max} (rs= −0.464).

Table 3 Exposure to panobinostat

		10 mg/m^2	15 mg/m^2	20 mg/m^2
Dose intensity (mg/day)	Mean±SD (range)	1.3±0.12 (1.2–1.4)	2.3±0.21 (2.0–2.5)	2.0±0.65 (1.3–3.0)
Relative dose intensity[a]	Mean±SD (range)	1.0±0.01 (1.0–1.0)	1.0±0.00 (1.0–1.0)	0.8±0.22 (0.5–1.0)

[a] Relative dose intensity = Actual dose intensity/Planned dose intensity

Efficacy

Stable disease for ≥4 months was observed in six patients (43%). No objective responses were confirmed. One female patient with ACC of the tongue had the longest exposure to panobinostat and received 10 mg/m^2 for 408 days (19 cycles). Another female patient with lung metastases from Ewing's sarcoma who was given 20 mg/m^2 had SD for 176 days, with a tumor shrinkage rate of 29.6% at the end of cycle 7.

Discussion

This phase I study of panobinostat in Japanese patients with advanced solid tumors demonstrated that the MTD of panobinostat given as an intravenous dose was 20 mg/m^2. Although only one patient experienced a DLT, the relative dose intensity in the 20 mg/m^2 cohort was low (0.8) and further dose escalation was deemed inappropriate. The result was consistent with a Western trial conducted in parallel, which had demonstrated that 20 mg/m^2 of i.v. panobinostat administered on Days 1, 8 of a 21-day cycle was recommended for future studies (unpublished data).

The most common adverse event was transient thrombocytopenia, which is a well-known class effect associated with HDAC inhibitors. Conventional cytotoxic agents usually cause bone marrow aplasia and megakaryocytopenia, whereas HDAC-inhibitors are thought to act via a distinct mechanism. Giver et al. observed an increase in

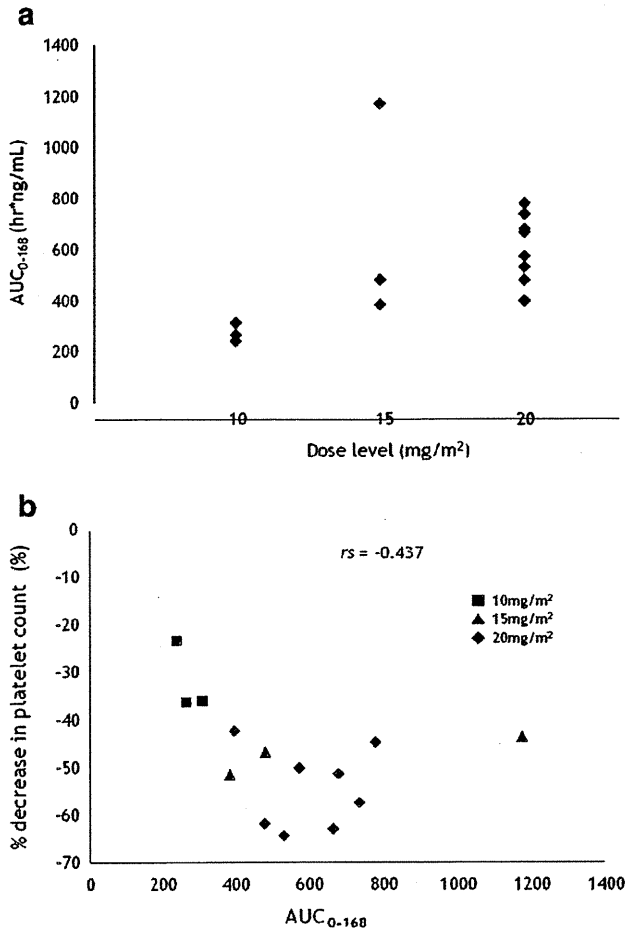

Fig. 2 **a**, scatter plot of $AUC_{0\text{-}168h}$ versus dose level. **b**, scatter plot of percent decrease in platelet counts on day 7/8 versus $AUC_{0\text{-}168h}$ during cycle 1. The percent decrease appeared to correlate with the AUC

Table 4 Summary of pharmacokinetic parameters according to initial dose cohort

dose level		t_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}168h}$ (hr*ng/mL)	$AUC_{0\text{-}inf}$ (hr*ng/mL)	CL (L/hr)	$t_{1/2}$ (hr)
10 mg/m^2 n=3	Day 1	0.5 (0.5–0.5)	272.0±42.58	273.2±36.50	273.7±36.49	54.1±5.61	16.8±1.17
	Day 8	0.5 (0.5–0.5)	317.7±125.90	333.2±78.36	309.3±67.50	48.8±9.54	17.4±4.62
15 mg/m^2 n=3	Day 1	0.5 (0.5–0.5)	496.0±226.38	680.3±431.10	433.6±68.44*	53.7±5.54*	16.9±2.97[a]
	Day 8	0.5 (0.5–0.5)	308.7±158.53	503.0±156.96	441.3±140.24	57.7±15.91	17.9±1.26
20 mg/m^2 n=8	Day 1	0.5 (0.5–0.6)	492.8±147.80	605.1±132.14	606.8±132.20	54.0±12.78	18.5±2.12
	Day 8**	0.5 (0.5–0.6)	526.8±101.77	755.6±225.33	791.4±235.52	42.0±14.06	36.9±19.05

Means±SD except for t_{max}, given as the median (range)

t_{max}, time of C_{max}; C_{max}, maximum panobinostat concentration in plasma; $AUC_{0\text{-}168h}$, area under the plasma panobinostat time-concentration curve from 0 to 168 h; $AUC_{0\text{-}inf}$, AUC from 0 to infinity; CL, systemic clearance of panobinostat; $t_{1/2}$, half-life of the terminal phase

* n=2

** n=5

megakaryocytes in bone marrow during panobinostat-induced thrombocytopenia in mice. They also found that the thrombocytopenia rapidly resolved after panobinostat was discontinued and suggested that the paradoxical increase in megakaryocytes was due to the suspension of megakaryocyte maturation caused by panobinostat [7]. Similarly, Matsuoka et al. demonstrated that another HDAC inhibitor (FR235225) causes thrombocytopenia and simultaneously increases megakaryocytes in rat spleen models. It was also speculated that FR235225 delays the maturation of megakaryocytes [8]. Recently, Bishton et al. showed that HDAC inhibitor-induced thrombocytopenia is not due to myelosuppression or reduced platelet lifespan, but to decreased platelet release from megakaryocytes [9]. Such mechanisms may underlie the rapid resolution of panobinostat-induced thrombocytopenia after treatment was discontinued in patients in the 20 mg/m^2 cohort (Fig. 1c). Two patients in the 20 mg/m^2 cohort required omission of the second dose in cycle 1 because of thrombocytopenia. Given that thrombocytopenia was dose-dependent and seemed to correlate with the platelet count at the baseline, it is recommended that patients with relatively low platelet counts at baseline be closely monitored for platelet depletion and considered for dose omission and reduction, as indicated, during treatment with HDAC inhibitors such as panobinostat. In a phase I study of oral panobinostat in Japanese patients with advanced solid tumors or CTCL, rapid recovery of panobinostat-induced thrombocytopenia was also reported [10].

Although QTcF prolongation was an issue identified in previous dose-finding studies using daily intravenous treatment with panobinostat [6], there were no abnormal QTcF prolongation events in this study, suggesting that once-weekly treatment is safe. There were no other unexpected or previously undescribed panobinostat-associated toxicities. When compared with the Japanese oral panobinostat study, fewer gastrointestinal disorders (especially diarrhea) in this study were reported [10]. Only one patient who received 20 mg/m^2 experienced a DLT (grade 3 elevation of γ-glutamyl transpeptidase for >7 days).

The pharmacokinetics of intravenous panobinostat in this study were comparable to those in Western patients who received once-weekly treatment in a 28-day cycle [5], suggesting no interethnic difference in the pharmacokinetic profile of panobinostat. A weakness of this study was that no biomarker was used to study pharmacodynamics. Histone acetylation is often measured as an index of HDAC inhibitor activity. In a Western study of intravenous panobinostat, acetylation levels of histone H3 in peripheral blood mononuclear leukocytes were measured at 7-day intervals [5].

The assessment of antitumor activity was not a primary objective of our study; however, six of the 14 patients had stable disease lasting more than 3 months. One female patient with ACC of the tongue continued treatment for more than 1 year with no attenuation of antitumor effectiveness. This finding is consistent with the results of a study of vorinostat performed by the National Cancer Institute Organ Dysfunction Working Group. The group reported favorable anticancer activity in five patients with ACC [11]. These results suggest that HDAC inhibitors might be an effective therapy for ACC, a disease that is refractory to chemotherapy and has no standard treatment. In a female patient with Ewing's sarcoma, tumor shrinkage fell just short of a PR. Although the underlying mechanisms cannot be fully defined, preclinical studies have suggested that HDAC inhibitors suppress the expression of EWS-Fli 1 chimeric protein, which is encoded by the chromosomal translocation t(11;22)(q24;q12) found in most (85% to >90%) cases of Ewing's sarcoma [12–15].

In conclusion, the present study demonstrated that intravenous panobinostat administered once daily on days 1 and 8 of a 21-day cycle was relatively safe and potentially effective in patients with advanced solid tumors. Although the MTD was not determined as defined in the protocol, it is feasible to conclude that 20 mg/m^2 was the MTD and it could be reasonably recommended as the starting dose for phase II clinical trials.

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Phase I study of concurrent real-time tumor-tracking thoracic radiation therapy with paclitaxel and carboplatin in locally advanced non-small cell lung cancer

Jun Sakakibara-Konishi[a], Satoshi Oizumi[a,*], Ichiro Kinoshita[b], Naofumi Shinagawa[a], Junko Kikuchi[a], Mototsugu Kato[c], Tetsuya Inoue[d], Norio Katoh[d], Rikiya Onimaru[d], Hiroki Shirato[d], Hirotoshi Dosaka-Akita[b], Masaharu Nishimura[a]

[a] First Department of Medicine, Hokkaido University School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan
[b] Department of Medical Oncology, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan
[c] Division of Endoscopy, Hokkaido University Hospital, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan
[d] Department of Radiology, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan

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ABSTRACT

Introduction: Although paclitaxel with carboplatin and thoracic radiotherapy has improved survival for patients with locally advanced unresectable non-small cell lung cancer (NSCLC), the optimal dose of paclitaxel has not been well defined in Japan. This study was conducted to determine the maximum tolerated dose (MTD) and recommended dose (RD) of paclitaxel in combination with carboplatin and concurrent real-time tumor-tracking thoracic radiation therapy (thoracic RTRT).

Patients and methods: Previously untreated patients with histologically confirmed, locally advanced unresectable NSCLC were eligible. Before treatment, gold markers were inserted into the lung and the mediastinum of all patients. RTRT comprised a total of 66 Gy at 2 Gy/fraction, 5 days/week, for 7 weeks. Patients received paclitaxel at a starting dose of 40 mg/m^2 followed by carboplatin at a fixed area under the curve (AUC) of 2, as a weekly regimen with RTRT. The dose of paclitaxel was escalated by 5 mg/m^2 per level.

Results: Eight patients with locally advanced unresectable NSCLC were enrolled and treated with two dose levels of paclitaxel (40 mg/m^2 and 45 mg/m^2), carboplatin (AUC = 2) and RTRT. No dose limiting toxicities (DLTs) were observed at Level 1 (paclitaxel, 40 mg/m^2 and carboplatin, AUC = 2). At Level 2 (paclitaxel, 45 mg/m^2 and carboplatin, AUC = 2), two of five patients experienced DLTs, in the form of esophagitis and discontinuation of chemotherapy more than twice. The MTD and RD of paclitaxel were thus defined as 45 mg/m^2 and 40 mg/m^2, respectively.

Conclusions: This phase I study was well tolerated and the RD of paclitaxel and carboplatin with RTRT is 40 mg/m^2 at AUC = 2, respectively. Further studies are warranted to evaluate the efficacy of this regimen.

1. Introduction

Lung cancer is a leading cause of malignancy-related death around the worldwide [1]. Although the use of concurrent chemotherapy and radiotherapy has improved survival for patients with locally advanced unresectable non-small-cell lung cancer (NSCLC) over the last two decades, cure rates are still low and treatment-related toxicities remain concern [2–4].

Paclitaxel is a microtubular inhibitor and arrests cell cycle in the G2-M phase, which is well recognized as the most radiosensitive phase. Paclitaxel reportedly enhances the radiosensitivity of cells *in vitro* [5]. Choy et al. reported that the maximum tolerated dose (MTD) of weekly paclitaxel with concurrent radiation was 60 mg/m^2 in phase I [6] and 1-, 2-, and 3-year overall survival rates were 60.6%, 33.3%, and 18.2%, respectively [7]. Moreover, they conducted a phase II study of paclitaxel at 50 mg/m^2, carboplatin at an area under the curve (AUC) of 2 and concurrent radiotherapy, revealing 1- and 2-year overall survival rates of 56.3% and 38.3%, respectively [8]. In Japan, several phase I trials of paclitaxel, carboplatin (AUC = 2) and radiotherapy have been conducted. Endo et al. reported that the MTD of paclitaxel was 45 mg/m^2 and dose limiting toxicity (DLT) was pulmonary toxicity [9]. Based on these results, the recommended dose (RD) of paclitaxel was considered to be 35–40 mg/m^2 in Japan. Compared to the results from the United States, the dose of paclitaxel remains low and has not been well investigated.

* Corresponding author. Tel.: +81 11 706 5911; fax: +81 11 706 7899.
E-mail address: soizumi@med.hokudai.ac.jp (S. Oizumi).

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Shirato et al. developed a real-time tumor-tracking radiation therapy (RTRT) which increases the potential efficacy of radiation by reducing the volume of normal tissue irradiated [10]. We have reported the feasibility of thoracic RTRT with insertion of gold markers into or near peripheral lung cancers using bronchoscopy. Local tumor response was achieved and maintained for 12 of 13 patients, with a median follow-up of 9 months [11]. Although radiation-induced pneumonitis was found in most of the patients with RTRT, these patients were asymptomatic. Moreover, RTRT with insertion of gold markers into the submucosal layer of the esophagus using endoscopy has also been shown to be feasible for the monitoring of the esophagus at risk [12,13]. Taken together, we hypothesized that use of the RTRT system with concurrent paclitaxel and carboplatin might reduce radiation-induced toxicities including radiation-pneumonitis and esophagitis, potentially allowing dose escalation of paclitaxel.

This phase I study investigated concurrent real-time tumor-tracking thoracic radiation therapy with paclitaxel and carboplatin in locally advanced NSCLC to evaluate feasibility and to determine the MTD and RD of paclitaxel.

2. Materials and methods

2.1. Patient eligibility

This phase I study was approved by the ethics committee at Hokkaido University School of Medicine. All subjects gave written informed consent prior to enrolling in this study.

Previously untreated patients with histologically confirmed locally unresectable stage IIB, IIIA or IIIB NSCLC were eligible. Patients were ≤75 years old and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 and measurable or assessable disease. Patients were required to have adequate bone marrow function (white blood cell count ≥4000/mm^3, hemoglobin count ≥9.5 g/dl, platelet count ≥100,000/mm^3), renal function (serum creatinine ≤2 times upper limit of institutional normal), liver function (aspartate aminotransferase and alanine aminotransferase ≤2 times upper limit of institutional normal, total bilirubin ≤1.5 mg/dl) and pulmonary function (arterial blood gases PaO_2 ≥70 Torr). Exclusion criteria were any of the following: (i) poorly controlled medical conditions, (ii) a history of other active malignancies, (iii) severe drug allergy, (iv) known hypersensitivity to the study drug or polioxyethilene, or (v) pregnancy or lactation.

2.2. Treatment plan

2.2.1. Chemotherapy

Patients received paclitaxel at a starting dose of 40 mg/m^2 followed by carboplatin at a fixed area under the curve (AUC) of 2 using the Calvert equation on days 1, 8, 15, 22, 29, 36, and 43 with concurrent RTRT. Paclitaxel dose levels were escalated by 5 mg/m^2 per level. Standard premedication for paclitaxel comprised dexamethasone 20 mg intravenous infusion (i.v.), ranitidine 50 mg i.v. and chlor-trimeton 10 mg i.v., administered 30 min before initiating paclitaxel infusion.

Toxicities were assessed using the National Cancer Institute-Common Toxicity Criteria version 2.0. Complete blood counts were monitored weekly during combined therapy. Doses of both carboplatin and paclitaxel were reduced to 50% of the full dose if grade 2 hematologic toxicity was observed. Chemotherapy was put on hold if any of the following developed: (i) grade 3 or 4 hematologic toxicities, (ii) fever ≥38 °C, (iii) PS 3 or 4. DLT was defined as any of the following: (i) persistent (≥3 days) grade 4 leucopenia, (ii) febrile neutropenia, (iii) discontinuation of weekly chemotherapy more than twice, (iv) RTRT ≥9 weeks, or (v) any grade 3 or 4 non-hematologic toxicities with the exception of anorexia, nausea, and vomiting.

Three patients were enrolled at the first dose level, and in the absence of DLTs, three patients were entered to the next dose level. If one of the 3 patients developed a DLT, then three additional patients were enrolled at the same level. If more than 1 of 3 or more than 2 of 6 patients had DLTs at a specific dose level, that dose level was defined as the maximum tolerated dose (MTD). The recommended dose (RD) was determined as the dose level that is one level bellow the MTD.

2.3. Radiotherapy

The procedures for insertion of gold markers have been provided previously [11]. Before radiotherapy, gold markers were inserted into the lung and the mediastinum of all patients using bronchoscopy and gastric endoscopy. RTRT began concurrently on day 1 with chemotherapy for all patients for 7 weeks. Gating was done for all patients. The setup of the RTRT system has been described previously [10,13]. Same method was used in this clinical trial.

Gross tumor volume was the primary and lymph nodes that had clinically tumor extension. Clinical target volume (CTV) margin for primary tumor was 6 mm for squamous cell carcinoma and 8 mm for adenocarcinoma according to Giraud et al. [14], and CTV margin for lymph nodes was 5 mm. CTV for elective nodal irradiation (CTV_E) included ipsilateral hilar lymph nodes, upper mediastinal lymph nodes, and subcarina lymph nodes. Supraclavicular lymph nodes were included to CTV_E when primary tumor located in upper lobe or main bronchus. When primary tumor located in lower lobe or invaded lower mediastinum, lower mediastinal lymph node was included to CTV_E. Lower mediastinal lymph node area was defined as the mediastinal area from the 5 cm below the carina to the caudal edge of 10th thoracic vertebra. Planning target volume (PTV) margin for CTV was 5 mm.

Initial target volume was PTV for CTV and CTV_E, and boost target volume was PTV for CTV. Initial target volume was irradiated 44 Gy in 22 fractions using AP-PA parallel opposing fields. Then boost target volume was irradiated 22 Gy in 11 fractions, sequentially, using oblique parallel opposing field usually. Heterogeneity correction was not used. Dose-volume histograms for lung and esophagus were calculated on the basis of first treatment planning CT. Esophageal V50 was determined as the percentage of total esophagus receiving dose >50 Gy. V20 was defined as the percentage of total lung volume receiving at least 20 Gy of radiation. Total lung volume was defined as the lung volume of both lungs minus the PTV.

Radiotherapy was withheld for any of the following reasons: (i) grade 4 leucopenia, (ii) grade 4 neutropenia, (iii) grade 3 thrombocytopenia, (iv) fever ≥38 °C, (v) grade 2 pneumonitis, (vi) PS 3, or (vii) grade 3 or 4 non-hematologic toxicities. If these toxicities were resolved, radiotherapy was reinstituted.

2.4. Response

Response was assessed using the RECIST (Response Evaluation Criteria in Solid Tumors) as published in 2000.

3. Results

Eight patients (6 men, 2 women) were enrolled on this study between February 2005 and December 2008. All patient characteristics are presented in Table 1. Median age was 68 years (range, 47–74 years). The ECOG PS was 0 for 5 patients and 1 for 3 patients. Underlying pathology was squamous cell carcinoma in 2 patients, adenocarcinoma in 4 patients and non-small cell carcinoma in 2

Table 1
Patient characteristics.

Total (*n*)	8
Gender (*n*)	
Male	6
Female	2
Age (years)	
Median	68
Range	47–74
PS	
0	5
1	3
Histology	
Squamous	2
Adenocarcinoma	4
Non-small	2
Clinical stage	
IIB	1
IIIA	2
IIIB	5

PS: ECOG performance status.

Table 2
Hematologic toxicities.

	Dose level					
	Level 1 (*n*=3)			Level 2 (*n*=5)		
	1/2[a]	3[a]	4[a]	1/2[a]	3[a]	4[a]
Leucopenia	3	0	0	1	4	0
Neutropenia	3	0	0	4	0	1
Anemia	1	0	0	1	0	0
Thrombocytopenia	0	0	0	1	0	0

[a] Toxicity (grade).

patients. One patient had clinically inoperable stage IIB, 2 had stage IIIA, and 5 had stage IIIB.

3.1. Toxicities of treatment

All patients received weekly carboplatin at a fixed AUC=2 and paclitaxel with a starting dose from 40 mg/m^2/week for 7 weeks with daily RTRT. Hematologic and non-hematologic toxicities are shown in Tables 2 and 3. Three patients were enrolled into Level 1 (carboplatin, AUC=2: paclitaxel 40 mg/m^2). Although mild toxicities developed in all patients at Level 1, there were no DLTs. Three patients were entered in Level 2 (carboplatin, AUC=2: paclitaxel, 45 mg/m^2). The first and second patients experienced no DLTs. However, the third patient showed grade 3 esophagitis and required intravenous infusion, which was considered a DLT. The percentage of total esophageal volume treated to >50 Gy (V50) has been identified as a significant predictor of acute esophagitis and

Table 3
Non-hematologic toxicities.

	Dose level					
	Level 1 (*n*=3)			Level 2 (*n*=5)		
	1/2[a]	3[a]	4[a]	1/2[a]	3[a]	4[a]
Nausea	1	0	0	0	0	0
Anorexia	0	0	0	1	0	0
Diarrhea	1	0	0	1	0	0
Esophagitis	2	0	0	3	1	0
Stomatitis	2	0	0	1	0	0
Rash	1	0	0	0	0	0
Pneumonitis	2	0	0	4	1	0
Hiccoughs	0	0	0	1	0	0
Fever	1	0	0	0	0	0
Neuropathy	0	0	0	1	0	0

[a] Toxicity (grade).

Table 4
Treatment response.

Dose level	CR	PR	SD	PD
Level 1 (*n*=3)	0	2	1	0
Level 2 (*n*=5)	0	3	1	1

CR: complete response. PR: partial response. SD: stable disease. PD: progressive disease.

it was reported that rates of acute severe esophagitis increased in patients with esophageal V50>40% [15]. V50 of this patient was 39.1%, which was relatively predictive of esophageal toxicity. One patient with larger V50 (67.1%) had grade 2 esophagitis and other 6 patients without grade 2/3 esophagitis had smaller V50 than 32.2%.

Two more patients were thus added at Level 2. No DLT was observed in the fourth patient. The fifth patient discontinued chemotherapy for 2 weeks due to persistent grade 3 leucopenia, which was considered as a DLT. The fifth patient was removed from the protocol and received radiotherapy alone. Grade 3 radiation pneumonitis developed in this patient 1 month after radiotherapy was finished. Patients with V20>30% reportedly encountered severe radiation pneumonitis [16,17]. V20 was 34% in this patient, which was predicted as the high risk of radiation pneumonitis, whereas, V20 was less than 20% in other 7 patients.

In summary, 2 of 5 patients at Level 2 experienced DLTs. Although enrollment of one additional patient was required to determine MTD, radiation pneumonitis in the fifth patient was severe, and the safety monitoring committee considered that the additional enrollment was difficult. Finally, the MTD and RD of paclitaxel were determined to be 45 mg/m^2 and 40 mg/m^2, respectively. No treatment-related deaths were encountered in this study.

3.2. Treatment response

All patients were assessable for treatment response (Table 4). Five of all eight patients showed partial response (PR), 2 had stable disease (SD), and 1 experienced progressive disease (PD). The patient with PD was the fifth patient at Level 2. This patient received chemotherapy only twice because of DLT and was removed from the protocol. Radiotherapy alone was continued but brain metastasis was found soon after radiotherapy was completed, resulting in treatment response being categorized as PD.

4. Discussion

We conducted a phase I study of paclitaxel, carboplatin and concurrent radiation using RTRT system in patients with locally unresectable advanced NSCLC. The MTD for paclitaxel and carboplatin at AUC of 2 was 45 mg/m^2, respectively. DLTs were grade 3 esophagitis and discontinuation of chemotherapy more than twice. RD for paclitaxel and carboplatin with RTRT was thus considered to be 40 mg/m^2 at AUC of 2.

The American Society of Clinical Oncology guidelines for the treatment of unresectable stage III NSCLC recommends combined-modality therapy with platinum-based chemotherapy and thoracic radiotherapy [18]. Two randomized phase III trials (West Japan Lung Cancer, Radiation Thoracic Oncology (RTOG) 9410) comparing sequential administration of chemotherapy and radiation with concurrent chemoradiotherapy in patients with unresectable stage III NSCLC showed longer median survival for patients receiving concurrent chemoradiotherapy than for those receiving sequential therapy [2,19]. Based on these results, the standard care for those patients is considered to be concurrent chemoradiotherapy. However, those phase III trials used old-generation agents/cisplatin-based chemotherapy regimens including mitomycin, vindesine, vinblastine and etoposide. During the last decade,

several new agents, so-called third-generation drugs have been developed including paclitaxel, docetaxel, irinotecan, gemcitabine, and vinorelbine. Combinations of platinum with these third-generation agents have proven more effective than old-generation platinum-based chemotherapies for advanced NSCLC [20,21]. The combination of these third-generation agents and platinum with radiation has thus been studied in locally advanced unresecatble stage III NSCLC.

Recently, two phase III trials in Japan have compared between the platinum/old-generation regimens and the platinum/third-generation regimens in combination with radiation. The Okayama Lung Cancer Group (OLCSG) conducted a randomized phase III study comparing between docetaxel/cisplatin (DP) and mitomycin, vindesine, cisplatin (MVP) with radiation [22]. In that phase III study, the DP arm tended to show better response and 2-year survival rates (78.8% and 60.3%, respectively) compared with the MVP arm (70.3% and 48.1%, respectively), although the differences were not significant. The West Japan Thoracic Oncology Group (WJTOG) conducted a phase III study comparing MVP, irinotecan/carboplatin, and paclitaxel/carboplatin in combination with concurrent radiation. They reported that paclitaxel (40 mg/m^2) and carboplatin (AUC = 2) with radiation (60 Gy) showed equally efficacious in the median survival time and 5-year survival rates (22.0 months and 19.8%, respectively) among three regimens, but again no significant difference was apparent [23]. Although third-generation regimens/platinum with radiation are considered as a standard regimen for unresectable NSCLC from these results, no clear differences in survival were identified between old and third generation regimens with radiation. We have previously reported that local tumor control was achieved for all 12 patients irradiated using RTRT system [11]. This is the first study to evaluate the safety and utility of combination of chemotherapy and RTRT system. This combination therapy may offer clinical favorable responses and survival.

In this study, paclitaxel and carboplatin with RTRT was well tolerated at Level 1, without DLTs. One patient developed grade 3 esophagitis at Level 2 that was considered a DLT. Choy et al. showed that esophagitis was the most significant toxicity in a phase II study of paclitaxel (50 mg/m^2), carboplatin (AUC = 2) and concurrent radiotherapy (66 Gy) [8]. Other phase I/II trails have also reported that radiation-induced esophagitis was evaluated as an objective measure of tolerance during the study, and 6–38% of patients developed grade 3/4 esophagitis [24]. Although radiotherapy using RTRT system might help to reduce the volume of irradiated esophagus, esophagitis should be still considered a major toxicity of this regimen and treatment should be performed with caution. The other DLT in our study was discontinuation of chemotherapy due to persistent grade 3 leucopenia. The profile of hematologic toxicities in our study was similar to that in other studies.

Lung toxicities can represent another of the major toxicities in addition to esophagitis in chemoradiotherapy. Several studies have shown that more than 10% of patients developed grade 3/4 pulmonary toxicity in phase I/II trials of paclitaxel, carboplatin and radiotherapy [8,25]. Endo et al. stopped dose escalation of paclitaxel in a phase I study due to concern over radiation pneumonitis [9]. One patient developed grade 3 pneumonitis in the present study: but that symptom was not considered a DLT because the pneumonitis occurred after the defined period for DLT estimation. However, we stopped additional patient enrollment to ensure safety. Finally, the MTD of paclitaxel in this study was determined as 45 mg/m^2, which was compatible with other study results from Japan [9], although it was less than the dose reported from the United States [8]. Differences in ethnicity may be related to the incidence of radiation-induced toxicities. Our hypothesis that RTRT might reduce the toxicities and allow dose escalation of paclitaxel was not established in this study, suggesting that individual variation has an impact on severity of toxicities.

In summary, concurrent RTRT with paclitaxel and carboplatin in locally advanced NSCLC was well tolerated. This might represent a new strategy for patients with locally advanced, unresectable NSCLC. A more extensive clinical study is warranted to verify the efficacy of this combined therapy.

Conflict of interest statement

The authors declare that they do not have any conflict of interest.

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THORAX

Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial

Takashi Ishida, Fumihiro Asano, Koichi Yamazaki, et al.

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Notes

ORIGINAL ARTICLE

Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial

Takashi Ishida,[1] Fumihiro Asano,[2] Koichi Yamazaki,[3] Naofumi Shinagawa,[3] Satoshi Oizumi,[3] Hiroshi Moriya,[4] Mitsuru Munakata,[1] Masaharu Nishimura,[3] for the Virtual Navigation in Japan (V-NINJA) trial group

See Editorial, p 1027

[1]Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan
[2]Department of Pulmonary Medicine, Gifu Prefectural General Medical Center, Gifu, Japan
[3]First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan
[4]Department of Radiology, Ohara General Hospital, Fukushima, Japan

Correspondence to
Fumihiro Asano, Department of Pulmonary Medicine, Gifu Prefectural General Medical Center, 4-6-1 Noishiki, Gifu 500-8717, Japan;
asano-fm@ceres.ocn.ne.jp

For author footnote see end of the article.

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ABSTRACT

Background Bronchoscopy using endobronchial ultrasound (EBUS) can help to diagnose small peripheral pulmonary lesions. However, although biopsy sites can be confirmed, a bronchoscope cannot be guided in EBUS. Virtual bronchoscopic navigation (VBN) can guide a bronchoscope with virtual images, but its value has not been confirmed.

Methods This prospective multicentre study examines the value of VBN-assisted EBUS for diagnosing small peripheral pulmonary lesions. 199 patients with small peripheral pulmonary lesions (diameter ≤30 mm) were randomly assigned to VBN-assisted (VBNA) or non-VBN-assisted (NVBNA) groups. A bronchoscope was introduced into the target bronchus of the VBNA group using the VBN system. Sites of specimen sampling were verified using EBUS with a guide sheath under fluoroscopy.

Results The diagnostic yield was higher for the VBNA than for the NVBNA group (80.4% vs 67.0%; p=0.032). The duration of the examination and time elapsed until the start of sample collection were reduced in the VBNA compared with the NVBNA group (median (range), 24.0 (8.7–47.0) vs 26.2 (11.6–58.6) min, p=0.016) and 8.1 (2.8–39.2) vs 9.8 (2.3–42.3) min, p=0.045, respectively). The only adverse event was mild pneumothorax in a patient from the NVBNA group.

Conclusions The diagnostic yield for small peripheral pulmonary lesions is increased when VBN is combined with EBUS.

Clinical trial number UMIN000000569.

Key messages

What is the key question?

- Can virtual bronchoscopic navigation improve the bronchoscopic diagnostic yield for small peripheral pulmonary lesions?

What is the bottom line?

- Bronchoscopy using endobronchial ultrasound (EBUS) can help to diagnose peripheral pulmonary lesions; however, EBUS cannot navigate the bronchoscope itself, so small lesions cannot always be reached.

Why read on?

- This multicentre, randomised study shows that the diagnostic yield for small peripheral pulmonary lesions is increased when virtual bronchoscopic navigation is combined with EBUS.

INTRODUCTION

Lung cancer is the leading cause of cancer death in Europe, the USA and Japan.[1–3] Although imaging modalities including CT, MRI and positron emission tomography have been applied, pathological findings remain the benchmark for a diagnosis of lung cancer. The increased frequency of high quality CT application has allowed the identification of much smaller and far more pulmonary lesions than before.[4]

Suspected malignant pulmonary lesions can be diagnosed by bronchoscopy, but the sensitivity of detecting small peripheral lung cancer varies from 36% to 86% depending on the size of the lesion.[5–7] According to the lung cancer diagnosis and treatment guidelines issued by the American College of Chest Physicians (ACCP),[8] the diagnostic sensitivity of bronchoscopy for peripheral pulmonary lesions is 78%, whereas that for lesions <2 cm is 34%. In comparison, the reported diagnostic sensitivity of transthoracic needle aspiration (TTNA) is 90%, and TTNA is recommended for diagnosing lesions <2 cm. Consequently, TTNA is frequently applied in many countries, but the incidence of complications is fairly high. The British Thoracic Society (BTS) guidelines state that the incidence of pneumothorax is 0–61%, with chest tube drainage required in 3.3–15%, intrapulmonary haemorrhage in 5–16.9% and haemoptysis in 1.25–5%.[9] The ACCP guidelines state with respect to bronchoscopy that, '...in expert hands, a radial probe US device can increase the diagnostic yield of FB while dealing with peripheral lesions of <20 mm in size. Its use can be considered prior to referring the patient for TTNA.' The given grade of recommendation is 2B.[8] Target lesions can be directly visualised by EBUS before attempting biopsies that raise the diagnostic yields for peripheral lesions[10]; reported diagnostic yields are 58.3–80%.[10–13] However, EBUS cannot navigate the bronchoscope itself, so lesions cannot be reached in 8–20.8% of cases.[11 13]

Navigational bronchoscopy has recently improved the diagnostic approach to peripheral small lesions. Electromagnetic navigation (EMN) is