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

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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 40mg/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 doxicities (DLTs) were observed at Level 1 (paclitaxel, 40mg/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 40mg/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], [3], [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 60mg/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 50mg/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.

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 ≥9.5g/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*

Chemotherapy: Patients received paclitaxel at a starting dose of 40mg/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 minutes 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℃, 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 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. Esophgeal 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℃, 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 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 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 (40mg/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 (66Gy) ([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 pclitaxel 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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Table 1. Patient Characteristics

Total (n)	8
Gender (n)	
Male	6
Female	2
Age (y)	
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)		
Toxicity (Grade)	1 / 2	3	4	1 / 2	3	4
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

Table 3. Non-Hematologic Toxicities

Dose Level	Level 1 (n=3)			Level 2 (n=5)		
Toxicity (Grade)	1 / 2	3	4	1 / 2	3	4
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

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