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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

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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.

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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